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Clinical response to chemotherapy in locally advanced breast cancer was not associated with several polymorphisms in detoxification enzymes and DNA repair genes

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ABSTRACT

The main aim of the present study was to investigate the association between several genetic polymorphisms (in glutathione S-transferase members and DNA repair genes) and clinical response to chemotherapy in locally advanced breast cancer. A sequential series of 101 patients were prospectively included in this study. Clinical assessment of treatment was accomplished by comparing initial tumor size with preoperative tumor size using revised RECIST guideline (version 1.1). Clinical response was regarded as a response or no response. There was no difference between non-responders and responders for the prevalence of genotypes of the study polymorphisms.

1. Introduction

Several studies investigated that the genetic polymorphisms of xenobiotic detoxification enzymes (such as glutathione S-transferase family) and DNA repair genes may be associated with susceptibility to breast cancer [1–6]. The additive effect of genetic variations of xenobiotic detoxification enzymes (*GSTM1*, *GSTT1*, and *GSTO2*) and DNA repair gene *XRCC1* on the susceptibility to breast cancer has been reported [4].

The goals of a preoperative chemotherapeutic approach in locally advanced breast cancer are to monitor tumor response and improve the rates of breast-conserving surgery. Therefore identification of factors involved in response is an important issue. It has been hypothesized that most inter-patient differences in the treatment efficacy are correlated with the genetic variability described by polymorphisms [7]. A growing body of evidence suggests that functional polymorphisms in metabolizing enzymes (such as glutathione S-transferases, GSTs) and DNA-repair proteins (such as X-ray repair cross complementing group 1; *XRCC1*) may have important implications for drug efficacy in cancer therapy [7]. To investigate the possible association of polymorphisms in detoxifying genes (*GSTT1*, *GSTM1*, *GSTZ1*, and *GSTO2*) and DNA repair genes (*XRCC1*, *XRCC6* and *XRCC7*) with clinical response to chemotherapy in locally advanced breast cancer patients, the present study was carried out.

2. Materials and methods

A sequential series of 101 patients were prospectively included in this study and were treated in the Department of Chemotherapy of Nemazi Hospital (Shiraz University of Medical Sciences, Shiraz, Iran) between September 2008 and July 2010. Patients were newly diagnosed, as locally advanced breast cancer. No patients had detectable metastatic disease before primary chemotherapy was instituted. Because Iranian population is one of the most heterogeneous populations [8–10], in the present study we included only Persians (Caucasians/Muslims) participants. The mean (SD) age of the patients was 47.4 (12.1) years (min and max: 26 and 81 years, respectively). The patients never used alcohol. This study was approved by the local ethics committee. Informed consent was obtained from all participants.

The patients received combination chemotherapy every 3 weeks (2–6 courses) with a regime containing cyclophosphamide (500 mg/m^2), adriamycin (50 mg/m^2) and 5-fluorouracil (500 mg/m^2) (=CAF treatment protocol) or docetaxel (75 mg/m^2) and adriamycin (50 mg/m^2), and cyclophosphamide (500 mg/m^2) (=TAC treatment protocol). In all cases, neither radiotherapy nor hormone therapy were applied before chemotherapy.

Clinical assessment of treatment was accomplished by comparing initial tumor size with preoperative tumor size using revised RECIST guideline (version 1.1) [11]. The largest diameter of tumor was taken as tumor size. Clinical response was assessed by physical examination using a caliper before each treatment cycle. Reduction in the tumor size by >30% or <30% were graded as a clinical response or no response, respectively [11].

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Table 1
Association between the study genetic polymorphisms and clinical response to chemotherapy in locally advanced breast cancer.

Polymorphisms	Non-responders	Responders	OR	95% CI	*P*-value
GSTT1 polymorphism					
Positive	25	50	1.0		
Null	9	17	0.94	0.36–2.41	0.905
GSTM1 polymorphism					
Positive	13	32	1.0		
Null	21	35	0.36	0.29–1.57	0.364
GSTO2 polymorphism (N142D, rs. 156697)					
NN	14	26	1.0		
ND	18	32	0.95	0.40–2.28	0.922
DD	2	9	2.42	0.45–12.7	0.297
GSTZ1 polymorphisms Glu32Lys (rs. 7975)					
Glu/Glu	22	43	1.0		
Glu/Lys	12	20	0.85	0.35–2.05	0.723
Lys/Lys + Glu/Lys	12	24	1.02	0.43–2.42	0.958
Gly42Arg (rs. 7972)					
Gly/Gly	31	63	1.0		
Gly/Arg	3	4	0.66	0.14–3.11	0.596
Promoter G-1002A					
GG	23	39	1.0		
AG	11	25	1.34	0.55–3.22	0.513
AA	11	28	1.50	0.63–3.57	0.359
XRCC1 polymorphisms Arg194Trp (rs. 1799782)					
Arg/Arg	26	56	1.0		
Arg/Trp	7	9	0.59	0.20–1.77	0.354
Arg/Trp + Trp/Trp	7	11	0.73	0.25–2.09	0.558
Agr399Gln (rs. 25487)					
Arg/Arg	20	32	1.0		
Arg/Gln	12	25	1.30	0.53–3.16	0.559
Gln/Gln	2	10	3.12	0.62–15.7	0.167
XRCC6 polymorphism (T991C, rs. 5751129)					
TT	20	27	1.0		
CT	11	31	2.08	0.85–5.12	0.108
CC	3	9	2.22	0.53–9.27	0.273
XRCC7 polymorphism (G6721T, rs. 7003908)					
GG	7	12	1.0		
TG	18	35	1.13	0.38–3.38	0.821
GG	8	20	1.45	0.42–5.05	0.551

The PCR conditions for determining the study polymorphisms were the same as that reported previously [7,12–15]. Evaluating the polymorphisms and laboratory quality control were the same as that reported previously [7,12–15].

To evaluate the association between polymorphisms and clinical response we used the odds ratio (OR) as statistical analysis method. An OR > 1.0 shows an increase and an OR < 1.0 shows a decrease in the prevalence of response. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) (version 11.5).

3. Results and discussion

Table 1 shows the prevalence of the study genetic polymorphisms among patients, stratified by their clinical response to chemotherapy (non-responders vs. responders). Statistical analysis revealed that there was no difference between non-responders and responders for the prevalence of genotypes of the study polymorphisms (Table 1).

Comparison between the present finding and previous reports [1–6], indicating that susceptibility for developing breast cancer and clinical response to chemotherapy are different multifactorial traits.

Because the ethnicity has some influence on association between genetic polymorphisms and risk of multifactorial traits [6,16,17], ethnicity may play a significant role(s) on association between genetic polymorphisms and clinical response of breast cancer to chemotherapy. Therefore, further research should examine the generalization of the present finding to other ethnic groups. Other studies are needed to elucidate the role of these polymorphisms with other candidate genes, as well as the effect(s) of environmental factors and treatment protocols in relation to clinical response.

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