GSTT1, GSTM1, and GSTP1 polymorphisms and chemotherapy response in locally advanced breast cancer

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ABSTRACT. The glutathione S-transferase (GST) family consists of phase II detoxification enzymes that catalyze the conjugation of toxic substances, such as chemotherapeutic agents, to glutathione. We examined whether GSTT1/GSTT1“null”, GSTM1/GSTM1“null” and GSTP1/Ile105Ile/GSTP1/Ile105Val polymorphisms are associated with different response rates to neoadjuvant chemotherapy in the treatment of stage II and III breast cancer. Forty Brazilian women with invasive ductal adenocarcinoma of the breast submitted to neoadjuvant chemotherapy, using 5-fluorouracil, epirubicin and cyclophosphamide, were genotyped for the GSTT1, GSTM1 and GSTP1 genes. Clinical...
response was assessed by RECIST criteria. Comparisons were made for the three genes alone and in pairs, as polymorphic and as wild-type combinations and polymorphic/wild-type combinations. We analyzed all possible combinations and their response rate. Patients with the $GSTT1/GSTP1$105Ile combination were found to have a significantly better response than $GSTT1^{null}/GSTP1$105Val ($P = 0.0209$) and $GSTT1/GSTM1$ ($P = 0.0376$) combinations. Analysis of all possible combinations showed the $GSTM1^{null}$ polymorphic genotype to be present in four, and the wild-type $GSTP1$105Ile in six of the combinations associated with the largest number of responding patients. We found that patients with the $GSTT1/GSTP1$105Ile wild-type combination had a significantly higher response rate to chemotherapy than patients with the respective polymorphic $GSTT1^{null}/GSTP1$105Val combination or patients with the wild-type $GSTT1/GSTM1$. The six gene combinations associated with the largest number of responding patients were found to contain the wild-type $GSTP1$105Ile and the polymorphic-type $GSTM1^{null}$. These specific combinations were virtually absent in the combinations with few responding patients.

**Key words:** Breast cancer; Polymorphism; Genetic; Drug therapy; Glutathione transferase