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Serum HER2 Level in Epithelial Ovarian Cancer

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Abstract

Introduction: The proto-oncogene HER2 plays a key role in the control of cellular proliferation. Its overexpression has been reported to be associated with a poor prognosis in cancer, particularly in breast cancer.

Materials and Methods: In the present study, serum HER2 levels were investigated in patients diagnosed with epithelial ovarian cancer. Serum HER2 levels were detected by an ELISA commercial kit in 51 patients and 33 healthy individuals.

Results: The mean serum HER2 level was found to be significantly higher in patients than healthy controls (P=0.005). In 29% of patients, serum HER2 levels were higher than the cut-off value. HER2 serum level was not associated with tumor stage at diagnosis.

Conclusion: Elevation of HER2 in a high proportion of patients with epithelial ovarian cancer further strengthens the importance of this molecule in the pathogenesis of ovarian cancer.

Keywords: Ovarian carcinoma, HER2, Serum, ELISA

Introduction

Ovarian cancer is the sixth most common cancer among women throughout the world. It is estimated that, worldwide, 190,000 new cases of ovarian cancer are diagnosed annually.[1] The epithelial type of ovarian cancer is present in more than 90% of all diagnosed cases of ovarian carcinomas.[2]

HER2 that is involved in the growth of both normal tissue and malignant tumors is a member of the epidermal growth factor receptor (EGFR).[3] Overexpression of HER2 protein is seen in 20-30% of breast cancer patients and is correlated with an aggressive disease and poor prognosis.[4,5] The monoclonal antibody trastuzumab (Herceptin) is routinely administered to HER2 overexpressing patients.[4]

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Overexpression of HER2 has also been reported in a significant proportion of ovarian cancer cases that has characterized a group of patients with aggressive phenotype.[6] However, this was not confirmed in other ovarian cancer studies.[7,8]

The conventional method for detecting HER2 overexpression is immunohistochemistry (IHC) that analyzes HER2 protein in tissue sections.[6] However, the intracellular binding region of HER2 is proteolytically released from the cell surface upon receptor activation and can be detected in both breast and ovarian cancer patients' sera.[8-13] Correlation of serum and tissue HER2 levels has been demonstrated in epithelial ovarian cancer.[9] Serological measurement of this soluble form of HER2 is an easier way for HER2 evaluation than the conventional IHC method.

The aim of the present case-control study was to analyze serum HER2 levels in the epithelial form of ovarian cancer. The correlation of serum HER2 levels with the clinical stage of the disease was also investigated.

Materials and Methods

HER2 serum assay

The study was approved by the Ethics Committee of Shiraz University of Medical Sciences. All participants were informed that blood samples would be used for serum analysis and their consent was obtained. Sera from 51 patients were collected, aliquoted and stored at -70ºC until use. From these, 25 samples were obtained prior to surgery and included in the study after pathological confirmation. The remaining 26 patients were known cases of epithelial ovarian cancer that had received chemotherapy or were currently undergoing chemotherapy at the time of serum analysis. Patients underwent surgery between 2005 and 2007 in the Departments of Gynecology at Faghihi or Zeinabieh Hospitals, Shiraz, Iran. Diagnosis of epithelial ovarian cancer was confirmed histopathologically. The stage of the disease was determined according to the International Federation of Gynecology and Obstetrics (FIGO) stage. Control subjects were 33 age-matched regional healthy women without history of a malignancy.

The levels of serum HER2 were determined by a commercial quantitative Enzyme- linked Immunosorbent Assay (ELISA) kit (Bender MedSystem, Austria) according to the manufacturer's instructions. Detection sensitivity of the kit was 0.06 ng/ml and the interassay coefficient of variation was 5.8%.

The cut-off level was calculated as mean + 2 SD of serum HER2 levels in 33 healthy controls. The sensitivity and specificity of the test were determined based on the following formula: Sensitivity = Number of subjects with the disease who tested positive/Total number of subjects with the disease. Specificity = Number of subjects without the disease who tested negative/Total number of subjects without the disease.

Statistical analysis

The data were analyzed using SPSS software (version 11.5.0; SPSS, Chicago, IL, USA). Student's t-test was used to compare HER2 levels in different groups. Findings were considered statistically significant at a *P* value less than 0.05.

Results

The serum levels of HER2 were checked in 51 patients with epithelial ovarian cancer. Samples from 25 of the patients were obtained prior to any treatment. Twenty six were under chemotherapy at the time of sampling. The mean serum HER2 levels between these two groups of patients were not significantly different (1.9 ±1.0 ng/ml in new cases vs. 2.5 ±1.6 ng/ml in known cases under chemotherapy, P=0.08). The mean serum HER2 level in patients (2.2 ±1.3 ng/ml; range: 0.4 to 7.8 ng/ml) was significantly higher than those of healthy controls (1.2 ±0.65 ng/ml; range: 0.2 to 3 ng/ml; P=0.005). There was no significant association between HER2 levels and tumor stage (P=0.17). The mean HER2 level was 2.7 ng/ml in FIGO stages I and II, and 2.4 in FIGO stages III and IV cancers.

Furthermore, the cut-off value of serum HER2

was 2.5 ng/ml. This cut-off value yielded a sensitivity of 29.1% and a specificity of 90.9%. Of 51 patients, 15 (29.1%) had HER2 levels higher than the cut-off value.

Discussion

The proto-oncogene HER2 is a transmembrane glycoprotein with tyrosine kinase activity that controls cell growth and differentiation.[3,4] HER2 is notable for its role as a targeted treatment in HER2 positive breast cancer patients. Overexpression of HER2 occurs in more than 20% of breast cancer patients and is negatively associated with prognosis.[5]

Although the impact of HER2 has been well established in breast cancer, in ovarian cancer, the percentage of tumors with HER2 overexpression varies widely according to the literature.[6-10] While up to 60% of patients in Turkey overexpressed HER2 protein, [8] this percentage was 6.6 % in a report by Tuefferd et al. from France.[7]

In the present study, we measured serum HER2 levels by ELISA, a method that is easier than the traditional IHC. The calculated cut-off value of serum HER2 approximated the cut-off value reported by Chen et al. in Taiwan [14] and those of Greece [11], but was lower than other studies.[12] Possible reasons for such discrepancies might be methodological differences or ethnic backgrounds. It was previously suggested that, in Asian women, the cut-off value of HER2 might be different from other populations.[14]

Our serum samples were obtained from two group of patients: i) new cases without any treatment, and ii) cases undergoing chemotherapy. The mean serum HER2 levels were not statistically different between these two groups. In this regard, it was shown that HER2 levels remain unchanged following chemotherapy in ovarian cancer.[6] Further studies with larger numbers of patients are required to exclude the possible minor correlation of serum HER2 levels with duration of treatment.

More than 20% of our patients had elevated HER2 serum levels. This percentage is higher than the report by McKenzie et al. (15%) [9] and lower than those of Yazici et al. (45%).[8] There was also no significant association between HER2 levels and tumor stage at diagnosis. Similarly, Meden et al.[10] and Yazici et al.[8] did not find such an association in ovarian cancer. Some follow up studies,[10] but not all,[7] have suggested that overexpression of HER2 is associated with shorter survival. This parameter was not assessed here.

In ovarian cancer, only one human study with anti-HER2 antibody has been published with discouraging results. However, in that trial, the antibody was administered as monotherapy, thus without the synergistic effect of chemotherapy.[15] In some populations, it is suggested that the low rate of HER2 overexpression reduces the potential utility of anti-HER2 therapy in ovarian cancer.[7,15] The increased levels of HER2 in more than 20% of our patients warrants further investigation on possible beneficial effects of this targeted therapy in HER2 positive individuals in Iran.

In conclusion, serum HER2 levels were elevated in a high proportion of our epithelial ovarian cancer patients. However, serum HER2 levels were not associated with tumor stage. The data further strengthen the importance of this molecule in the pathogenesis of ovarian cancer and warrant larger studies to determine the association of serum HER2 levels with tumor stage or other disease characteristics.

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