Research Article

HER2/Neu Expression was Different between Benign, Borderline and Malignant Epithelial Ovarian Tumors

Ekspresi HER2/Neu Berbeda pada Tumor Ovarium Epitelial Tipe Jinak, Borderline dan Ganas

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Abstract

Objective: To determine the difference of HER2/neu expression in benign, borderline and malignant epithelial ovarian tumor.

Method: An analytic cross-sectional study was performed on 49 samples of epithelial ovarian cases which were divided into three groups: twelve cases of benign epithelial ovarian tumor, 9 cases of borderline epithelial ovarian tumor and 28 cases of malignant epithelial ovarian tumor. Paraffin embedded tissue samples was cut, stained with HER2/neu imunohistochemistry and examined in Pathology Laboratory at Sanglah Hospital. The other data was collected from medical record samples. The data was analysed using One Way Anova test and Chi-square test with level of confidence $\alpha = 0.05$.

Result: There were 13 cases (46.43%) of the HER2/neu over expression in malignant epithelial ovarian tumors, 2 cases (22.22%) of the HER2/neu over expression in borderline epithelial ovarian tumors and 1 case (9.09%) of the HER2/neu over expression in benign epithelial ovarian tumors. With $p = 0.048$ ($p < 0.05$), there are differentiation of HER2/neu expression in benign, borderline and malignant epithelial ovarian tumors.

Conclusion: In this study HER2/neu expression was different between benign, borderline and malignant epithelial ovarian tumors.

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Keywords: benign epithelial ovarian tumor, borderline epithelial ovarian tumor, HER2/neu, malignant epithelial ovarian tumor, ovarian cancer.

Abstrak

Tujuan: *Untuk mengetahui adanya perbedaan ekspresi HER2/neu pada tumor ovarium epitelial jinak, borderline dan ganas.*

Metode: *Merupakan uji potong lintang analitik. Jumlah sampel adalah sebesar 49 sampel di mana 12 kasus dengan tumor ovarium epitelial tipe jinak, 9 kasus dengan tumor ovarium epitelial tipe borderline dan 28 kasus dengan tumor ovarium epitelial tipe ganas. Blok parafin sampel dipotong ulang, dilakukan pengecatan imunohistokimia HER2/neu dan diperiksa ekspresi HER2/neu pada Laboratorium Patologi Anatomi Rumah Sakit Sanglah. Sedangkan data lain penelitian diperoleh dari rekam medis sampel. Dari data yang terkumpul dilakukan uji One Way Anova untuk karakteristik sampel, kemudian dilakukan analisa data dengan uji Chi-square dengan tingkat kemaknaan $\alpha = 0,05$.*

Hasil: *Overekspresi HER2/neu pada tumor ovarium epitelial tipe ganas adalah sebanyak 13 kasus (46,43%) dibandingkan dengan over ekspresi HER2/neu pada tumor ovarium epitelial tipe borderline yang hanya sebanyak 2 kasus (22,22%) dan tipe jinak yang hanya sebanyak 1 kasus (9,09%). Dengan nilai $p = 0,048$ ($p < 0,05$) maka terdapat perbedaan ekspresi HER2/neu pada tumor ovarium epitelial tipe jinak, borderline dan ganas.*

Kesimpulan: *Berdasarkan hasil penelitian didapatkan bahwa terdapat perbedaan ekspresi HER2/neu pada tumor ovarium epitelial tipe jinak, borderline dan ganas.*

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Kata kunci: *HER2/neu, kanker ovarium, tumor ovarium epitelial tipe jinak, tumor ovarium epitelial tipe borderline, tumor ovarium epitelial tipe ganas.*

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INTRODUCTION

Ovarian cancer is a malignancy of the female ovaries and one of the main causes of death in the world besides cervical cancer. In the field of gynecologic cancer, a malignancy of the ovary is the biggest clinical challenge. But until now pathogenesis or cause of ovarian cancer is not yet clear, precautions that can be done and treatment of ovarian cancer has not been satisfactory. Often patients come in the advance stage so that the operative treatment or chemotherapy can not give much hope to the patient.

Major cause of ovarian cancer is still a matter of debate, but there are some risk factors that have been widely studied and is thought to be a trigger of the ovarian cancer include genetic factors, age, parity, race, and family history of breast cancer and ovarian cancer.[1-3] At the biomolecular level genetic

mutations occur, one of which occurred amplification of oncogenes that results in over expression of some proteins. Human Epidermal Growth Factor Receptor 2 (HER2) oncogene, which is also known as HER2/neu, ErbB2 or c-ErbB2, presumably plays an important role in the carcinogenesis process. HER2/neu is a receptor on the cell surface that have the same structure as the Epidermal Growth Factor Receptor (EGFR), is located on chromosome 17q21 which encodes a trans membrane glycoprotein via tyrosine kinase activity. Her2/neu bonding with ligand will trigger phosphorilation and dimerization process so that the signal transduction mechanism of activation can be submitted through Phosphoinositides 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) to trigger cancer cell proliferation and blood vessel formation (angiogenesis).[4] In breast tumors, over expression of HER2/neu around 25% of all breast cancer cases. HER2/neu has been shown to play a role in carcinogenesis and prognosis of breast carcinoma and has also developed a method for HER-2/neu targeted therapy.

On ovarian tumors, HER2/neu over expression varies between 9% to 32%. However, the role of HER2/neu in ovarian cancer has not been widely studied. HER-2/neu role in carcinogenesis and prognosis of ovarian cancer is still controversial.[5] By knowing the HER2/neu expression in ovarian tumors might be expected to reveal the role of HER2/neu in ovarian tumor in carcinogenesis, prognostic and therapeutic targets in the future.

METHOD

This study uses cross sectional analytic study. Sample is drawn from populations by consecutive sampling. Subjects were patients of epithelial ovarian tumors in Sanglah Hospital from January 2011 to April 2012, who met the inclusion criteria. The inclusion criteria for the study were as follows: laparotomy surgery at Sanglah, histopathologic examination in Anatomical Pathology Laboratory Sanglah, medical records of patients in the Medical Record Sanglah Installation and paraffin blocks of patients are still there and in good condition for HER2 immunohistochemistry examination/neu.

This study was conducted from January 2012 to December 2012 and obtained reasonable populations of epithelial ovarian tumors of 63 patients, of which 9 patients did not meet the inclusion criteria and 5 patients dropped out. Thus, the number of patients who underwent the study until the end

were 49 patients with epithelial ovarian tumors. Then 49 samples of paraffin blocks and secondary data were collected from the Pathology Anatomy and Obstetrics and Gynecology Department, Faculty of Medicine, Udayana University/Sanglah Hospital. The samples consisted of 12 cases with benign epithelial ovarian tumors, 9 cases with borderline epithelial ovarian tumors and 28 cases with malignant epithelial ovarian tumors. HER2/neu immunohistochemistry examination was performed on the samples that have been collected was done, then examined by a pathologist at Pathology Anatomy Department of Sanglah Hospital to determine the expression of HER2/neu. The data collected were processed using the computer program SPSS for Windows version 17.0.

RESULT

In this cross sectional analytic study characteristics diference sample test was done between groups with One Way Anova test for maternal age and parity variables. Results of the analysis are presented in Table 1 below.

Table 1. The Mean Age and Parity Distribution of Epithelial Ovarian Tumors in Group Benign, Borderline and Malignant.

Variable	Epithelial Ovarian Tumor			p
	Benign	**Borderline**	**Malignant**	
Age	39.67±12.22	48.11±12.90	46.46±10.43	0.685
Parity	1.92±1.31	2.56±1.74	1.79±1.16	0.302

In Table 1, it is indicated that between benign, borderline and malignant group of epithelial ovarian tumors, did not differ in age, with p = 0.685 (p > 0.05), as well as the parity variables with p = 0.302 (p > 0.05).

Chi-Square test was used to determine difference in HER2/neu expression between benign, borderline and malignant group of epithelial ovarian tumors. Significance of analysis results are presented in Table 2.

In Table 2 indicated that HER2/neu over expression in epithelial ovarian tumors are malignant type were 13 cases (46.43%), borderline type which only 2 cases (22.22%) and benign type that only 1 case (9, 09%). With p = 0.048 (p <0.05) then there is a difference in HER2/neu expression in benign, borderline and malignant epithelial ovarian tumors.

Table 2. Difference of HER2/neu Expression in Benign, Borderline and Malignant Epithelial Ovarian Tumor.

		Over expression HER2/neu		x^2	p
		(+)	(-)		
Epithelial Ovarian Tumor	Malignant group	13	15		
	Borderline group	2	7	6.089	0.048
	Benign group	1	11		

DISCUSSION

In this study, we examined HER2/neu immunohistochemistry in 49 samples of epithelial ovarian tumors. The samples consisted of 12 cases with benign epithelial ovarian tumors, 9 cases with borderline epithelial ovarian tumors and 28 cases with malignant epithelial ovarian tumors.

The mean age in the group of benign epithelial ovarian tumors are 39.67 ± 12.22 years, borderline was 48.11 ± 12.90 years and malignant was 46.46 ± 10.43 years, which was not statistically significant, p = 0.685 (p> 0,05). Similarly, the mean parity in the group of benign epithelial ovarian tumors was 1.92 ± 1.31, borderline was 1.74 ± 2.56 and malignat was 1.79 ± 1.16, which was also statistically not significant, p = 0.302 (p> 0,05). This result is similar according to a multicentre study of 320 patients in France, where the HER2/neu status has no significant impact on the patient's age or parity.[6]

After examination of the HER2/neu immunohistochemistry showed that the HER2/neu over expression in malignant epithelial ovarian tumors in this study was 46.43% (13 of 28 cases), borderline epithelial ovarian tumors was only 28.57 % (2 of 9 cases), and benign epithelial ovarian tumors was only 9.09% (1 of 12 cases).

A clinical study on the prevalence and prognosis relationships HER2/neu over expression in epithelial ovarian cancer cases, showed HER2/neu over expression by 13.9% (27 of 194 cases) of epithelial ovarian cancer. It was concluded in this study that over expression of HER2/neu associated increase in ovarian cancer progression and death.[7]

An article review of previous studies since 1989 show that HER2/neu over expression in malignant epithelial ovarian tumors ranged from 1.8 to 76%. In the article it was also found that HER2/neu over expression in borderline epithelial ovarian tumors ranged from 10% to 66%. HER2/neu over expression percentage range is very wide it is associated with many factors, such as sample size, type of monoclonal antibody used, the intensity of staining, the tissue examined and the definition of HER2/neu over expression.[8]

A study to determine the prognostic value and HER2/neu over expression in 44 cases of benign epithelial ovarian tumors and 124 cases of epithelial ovarian cancer, showed that there was no over expression in benign ovarian tumors and HER2/neu over expression in epithelial ovarian cancer was 24.2%. It is associated with advanced stage ovarian cancer, clear cell and undifferentiated type and suboptimal surgery. HER2/neu over expression simultaneously associated with ovarian cancer prognosis is worse.[9]

A multicenter study in France involving 320 patients to investigate the HER2/neu status in ovarian carcinoma by immunohistochemistry was 12.8% (41 cases). They also do a review on the previous choice studies since 1994, found the number of HER2/neu over expression ranged from 8% to 66%. Several explanations could explain the wide variation among others: the difference detection methods (immunohistochemistry, FISH (fluorescence in-situ hybridization) and chromogenic in situ hybridization), differences in materials and technique variations CPI (CB-11, Hercep Test or non-commercial antibody). This study is the first large-scale multicenter ever done.[6]

While the study of HER2/neu over expression in benign serous epithelial ovarian tumor benign found that HER2/neu over expression was 12.5% (2 cases out of 15 samples).[10] However, in previous studies on benign epithelial ovarian tumors, HER2/neu over expression was not obtained.[11,12]

The main result in this study is that HER2/neu expression was different between benign, borderline and malignant epithelial ovarian tumors, with p = 0.048 (p < 0.05). Thus, HER2/neu in ovarian cancer is interesting to study due to its potential

role in the pathophysiology, prognosis factors and targeted pharmacotherapy.[8] However, these results still could not determine HER2/neu over expression as the cause of ovarian cancer because the relationship of HER2/neu over expression and ovarian cancer was inconsistent in previous studies. This study also could not determine the effect of Transtuzumab use as a therapeutic option in patients with ovarian cancer with HER2/neu over expression, because clinical trials should be performed in order to provide adequate evidence. While the role of HER2/neu over expression as a prognostic factor still requires studies that compare between HER2/neu over expression with prognostic factors in ovarian cancer, such as stage, histological type or differentiation of ovarian cancer cells.

The weakness of this study is that cross-sectional analytical method can only determine whether there is a difference between a group and can not know the difference or the strength of the relationship between the study variables. Then this study used secondary data where data was incomplete, especially when looking for family history data with breast cancer and ovarian cancer. So that a family history of breast cancer and ovarian cancer as a risk factor for ovarian cancer can not be analyzed.

CONCLUSIONS

HER2/neu expression was different between benign, borderline and malignant epithelial ovarian tumors.

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