Research Article

HE4 Levels in Ovarian Cancer-Resistant Menopausal Women

Kadar HE4 pada Perempuan Menopause yang Resisten Kanker Ovarium

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Abstract

Objective : To analyse the predictive value of HE4 in ovarian cancer patients according to their resistance and menopausal status.

Methods : Thirteen premenopausal and twenty-five menopausal ovarian cancer patients were measured for HE4 levels measured using automated chemiluminescent microparticle immunoassay ARCHITECT HE4. Patients categorized into resistant and non-resistant after six cycles of chemotherapy in addition to their clinical symptoms and ultrasound image of cancer.

Results : The mean HE4 levels were higher in the resistant group compared with a non-resistant group (274.97 pmol/l vs 128.83 pmol/l; p=0.015). Five menopausal resistant women with HE4 levels >140 pmol/l compared with two women in the non-resistant group. In the pre-menopause group, eight resistant women with HE level >70 pmol/l whereas four women in the non-resistant group. HE levels in menopausal and premenopausal for both ovarian cancers resistant and non-resistant were not significantly different (p>0.05).

Conclusions : HE4 levels in resistant ovarian cancer patients are higher compared with non-resistant but do not predict ovarian cancer resistance based on patient menopausal status.

Keywords : HE4, ovarian cancer, resistance.

Abstrak

Tujuan : *Untuk menganalisis nilai prediktif HE4 pada pasien kanker ovarium berdasarkan resistensi dan status menopausenya.*

Metode : *Dilakukan pengukuran kadar HE4 menggunakan metode microparticle immunoassay ARCHITECT HE4 terhadap pasien kanker ovarium terdiri atas 13 perempuan premenopausal dan 25 perempuan menopause. Pasien dikategorikan menjadi resisten dan tidak resisten setelah 6 siklus kemoterapi selain gejala klinis dan gambar USG.*

Hasil : *Rerata kadar HE4 rata-rata lebih tinggi pada kelompok yang resisten dibandingkan dengan kelompok yang tidak resisten (274,97 pmol/l vs 128,83 pmol/l; p=0,015). Terdapat 5 perempuan menopause yang resisten kanker ovarium dan 2 perempuan dalam kelompok yang tidak resisten dengan kadar HE4 >140 pmol/l. Pada kelompok premenopause, 8 perempuan yang resisten dengan tingkat HE >70 pmol/l sedangkan 4 perempuan dalam kelompok tidak resisten. Kadar HE dalam menopause dan premenopause untuk kedua kanker ovarium resisten dan tidak resisten tidak berbeda secara signifikan (p>0,05).*

Kesimpulan : *Kadar HE4 pada pasien kanker ovarium lebih tinggi daripada tidak resisten tetapi tidak memprediksi resistensi kanker ovarium berdasarkan status menopause pasien.*

Kata kunci : *HE4, kanker ovarium, resistensi .*

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INTRODUCTION

Ovarian cancer is the fifth leading cause of death in women.[1] Most ovarian cancer patients are diagnosed at an advanced stage (FIGO stage III-IV); hence, the 5-year survival rate in ovarian cancer depends on the stage, at early stage of ovarian cancer survival rate of about 80-90% while in advanced stage it is only about 30%.[2] Despite advances in treatment, the survival rate remains unchanged. Therefore, an understanding of the pathogenesis of ovarian neoplasm molecules is needed so that new therapeutic targets or biomarkers for early detection of ovarian cancer or ovarian neoplasm can be identified and improved the treatment outcomes.[3]

Cancer antigen 125 (CA125) is mostly used as a serological biomarker in routinely for managing patients with gynecologic cancer[4] but limited due to its sensitivity and specificity. Human epididymis protein-4 (HE4) is a new promising marker

that over expressed in healthy tissue and ovarian cancer.[5] Its expression does not depend on CA125.[6] Serum HE4 is more specific than CA125 in differentiating tumors malignancy.[7]The serum HE4 level may have prognostic value for evaluating treatment response, including chemoresistance. The objective of this study is to analyse the predictive value of HE4 in ovarian cancer patients according to their resistance and menopausal status.

METHODS

Ovarian cancer patients, premenopausal and menopausal, were enrolled in a cross-sectional study was conducted at affiliated hospitals of the Obstetrics and Gynecology Department of Universitas Hasanuddin, Makassar, South Sulawesi. Patients were categorized as resistant and non-resistant after six cycles of chemotherapy in addition to their clinical symptoms and ultrasound image of cancer. HE4 levels measured using automated chemiluminescent microparticle immunoassay ARCHITECT HE4 (Fujirebio Diagnostics, Abbott's, UK) according to the manufacturer's instruction. Mann Whitney test used to compare mean HE4 levels between resistant and non-resistant patients. A *p*-value <.05 was considered statistically significant. Written informed consent obtained from all pregnant women and the Health Research Ethics Committee Faculty of Medicine Universitas Hasanuddin Makassar approved the study.

RESULTS

Table 1 shows patients at the age of menopause was 28(73.7%) women, and in 10 (26.3%) women were premenopausal, 23(60.6%) women were multiparous, 24(63.2%) women not using any methods of contraception, and 33(86.8%) were married. Histological findings show the type of ovarian cancer consisted of serous (63.2%) and mucinous (35.8%) with 78.9% of patients in advanced FIGO stage (III-IV).

A significant difference in HE4 levels between resistant and non-resistant ovarian cancer show in table 2. The mean HE4 levels were higher in the resistant group compared with a non-resistant group (274.97 pmol/l vs 128.83 pmol/l; p = 0.015). Five menopausal resistant women with HE4 levels >140 pmol/l compared with two women in the non-resistant group. In the pre-menopause group, eight resistant women with HE level >70 pmol/l whereas four women in the non-resistant group. HE levels in menopausal and premenopausal for both ovarian cancers resistant and non-resistant were not significantly different ($p>0.05$).

Table 1. Demographic Characteristics

Characteristics	n	%
Age		
Premenopausal	13	34.2
Menopausal	25	65.8
Parity		
Nulliparous	8	21.1
Primipaous	4	10.5
Multiparous	26	68.4
Contraceptive methods		
Pills	3	7.9
DMPA	10	26.3
IUD	1	2.6
None	24	63.2
Marital status		
Married	33	86.8
Not married	5	13.2
Histology		
Serous	24	63.2
Mucinous	14	36.8
FIGO stage		
I-II	8	21.1
III-IV	30	78.9

Table 2. HE4 Level Based on Ovarian Cancer Resistance

HE4 level (pmol/l)	Resistant (n=19) n%	Non-resistant (n=19) n%	*P-value*	RR	95%CI
Mean	274.97	128.83	0.015	-	214-259
Menopause					
>140	5(71.4)	2(28.6)	0.085	2.143	0.954-4.788
≤140	6(33.3)	12(66.7)			
Pre-menopausal					
>70	8(66.7)	4(33.3)	0.385	0.33	0.150-0.742
≤70	0	1(100)			

DISCUSSION

Our study shows that the mean HE4 levels in women with ovarian cancer resistant at menopausal age were higher compared with women with premenopausal non-resistant ovarian cancer. Similar to our findings, the previous study that shows the mean HE4 plasma in women with ovarian cancer was 225.83 pmol/l. Post therapy, 91.3% of resistant ovarian cancer patients had elevated HE4 levels up to 2-fold compared with HE4 levels before therapy.[8] Because the mean age of our study was women in the menopausal period, the HE4 levels found in women non-resistant ovarian cancer were different from findings of the previous studies.

HE4 levels are affected by age. Urban et al recommend the use of age-based thresholds per decade to achieve 95% HE4 specificity. The proposed threshold range is 41.4 pmol/l μm for women aged 30 years to 82.1 pmol/l for women aged 80 years.[9] Urban In addition to age, HE4 levels are also affected by pregnancy. During pregnancy, HE4 levels decreased compared with non-pregnant premenopausal women. Women with late menarche and smoking have higher HE4 levels. While the menstrual cycle, endometriosis, use of contraceptives containing estrogen and progestin does not alter serum HE4 levels.[10]

Our study also found no significant association between HE4 levels and ovarian carcinoma resistance in premenopausal patients. However, a review in 28 clinical studies found that HE4 levels decreased immediately after therapy but again increased when recurrence occurred. Failure of HE4 levels to return to normal levels after administration of therapy indicates a poorer prognosis. When comparing four markers, including CA 125, HE4, MMP-7, and mesothelin were monitored in patients with advanced-stage ovarian cancer after surgery and chemotherapy, HE4 levels increased in 4.5 months of recurrence. In patients with elevated levels of CA 125, HE4 levels have increased before CA125 elevated. In patients with negative recurrence according to CA 125 levels and imaging show, HE4 levels were higher than the cut-off value.[11]

HE4 has been known to trigger migration and adhesion of ovarian cancer cells. In an in vitro study, HE4 knockdown leads to inhibition of tumor growth. HE4 overexpression in endometrial cancer cell lines induces in vivo and in vitro cell proliferation. These findings support the role of HE4 in tumor progression. HE4 act as a protease inhibitor, decreasing serene protease activity Prss35 and Prss23, which degraded type I collagen accumulating in renal fibrosis. Fibrosis was inhibited by three mouse models when given HE4 neutralizing antibodies. [12] these findings suggest that HE4 potentially as a therapeutic target in renal fibrosis. HE4 also has an additional role in maintaining innate immunity.

Published the first prospective controlled study evaluating the sensitivity and specificity of HE4 in detecting resistant ovarian cancer. From 68 patients with ovarian cancer, the sensitivity and specificity of HE4 in predicting resistant ovarian cancer with a cut-off 70 pmol/l were 73% and 100%, respectively.[13] Prospectively enrolled 73 patients with resistant ovarian cancer and found that HE4 level 250 pmol/l as the cut-off had 52% sensitivity and 93.8% specificity in predicting disease resistance.[14] Another study suggests HE4 has prognostic value in ovarian cancer resistance with a superior sensitivity compared to CA125 (91.3% vs 52.7%, respectively).[8] HE4 had a sensitivity of 96.9% in another study.[15]

In our study, the sensitivity and the specificity was 73.68% and 68.2% according to a cut-off of 140 pmol/l as the mean HE4 levels in all women with ovarian cancer resistant in menopausal. This value means that HE4 levels can be relied upon to detect the risk of ovarian cancer resistant. The difference in specificity and sensitivity of some previous studies may be due to the difference in cut-off used in the study. In previous studies, HE4 has a high specificity and sensitivity in menopausal ovarian cancer.[16] Higher sensitivity and specificity (98% and 100%, respectively) of HE4 compared with CA125 between normal women and women with pelvic mass due to gynecologic cancer (cancer (ovarian, endometrial, cervical).[17] ROMA's prediction of sensitivity to ovarian cancer was higher in menopause compared with premenopausal with 94% sensitivity and 75% specificity.[18]

Despite the progress of ovarian cancer treatment, most patients will recur after a complete clinical response and most patients is incurable. As a result, treatment of resistant

is an essential aspect of the overall management of epithelial ovarian cancer. In epithelial ovarian cancer resistant, HE4 levels increase significantly in patients receiving platinum-based adjuvant chemotherapy.[19] Introducing HE4 as a new marker for predicting platinum-sensitivity and interval optimal cytoreduction is promising.[20]

Although this study showed no association between HE4 levels and the risk of resistant ovarian cancer, the results of the study should be interpreted with caution due to the limitations of our study. The first is a relatively small sample size so that the results of this study may be influenced by chance. Although we have controlled confounding variables with exclusions, other confounding variables such as clinical stage, degree, CA125 level, and post-chemotherapy disease residue were not analyzed.

CONCLUSION

In conclusion, HE4 levels in resistant ovarian cancer patients are higher compared with non-resistant but do not predict ovarian cancer resistance based on patients menopausal status.

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