RESEARCH ARTICLE

Does Human Epididymis Protein 4 (HE4) Have a Role in Prediction of Recurrent Epithelial Ovarian Cancer

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Abstract

Background: Despite the fact that ovarian cancer is the seventh most common cancer in women worldwide and the fifth leading cause of cancer death, It is the most common cause of death due to reproductive cancers in Thailand where epithelial ovarian cancer (EOC) is commonly found. According to a Thai statistical analysis in 2010 by the Department of Medical Services, epithelial ovarian cancer was the sixth most common cancer in Thailand from 2001to 2003.The incidence of 5.1 per 100,000 women per year. Human epididymis protein 4 (HE4) is a novo diagnostic tumor marker for EOC. The combination of HE4 and carcinoma antigen 125 (CA 125) is a tool for detecting epithelial ovarian cancer (EOC) better than using CA 125 alone. Therefore, the researcher is interested in HE4 does have a role to predict recurrent epithelial ovarian cancer. Materials and Methods: The patients who had complete response after diagnosed with epithelial ovarian cancer by pathology, FIGO stage 3 or more had been treated through surgery and chemotherapy at the Sunpasitthiprasong Hospital from June 2014 until March 2016. The patients were followed up every three months, using tumor marker (CA 125, HE4,Carcinoma antigen 19-9) together with other checkup methods, such as rectovaginal examination, CXR every year and other imaging as indication. Afterwards, the data was analyzed for the ability of HE4 to detect recurrence of epithelial ovarian cancer. Results: In 47 patients in this study follow-up for 22 months after complete response treatment from surgery and chemotherapy in epithelial ovarian cancer, 23 had recurrent disease and HE4 titer rising .The patients with recurrent epithelial ovarian cancer demonstrated high levels of both HE4 and CA125 with sensitivity of 91.3% and 52.7% respectively, specificity of 87.5% and 95.6% and positive predictive values of 87.5% and 85.7% . HE4 can predict recurrent epithelial ovarian cancer (p-value=0.02242). Comparing HE4 and CA125 in predicting recurrent epithelial ovarian cancer HE4 had more potential than CA125 (p-value =0.8314). Conclusions: The present study showed HE4 to have a role in predicting recurrent epithelial ovarian cancer and HE4 is potentially better than CA125 as a marker for this purpose.

Keywords: Epithelial ovarian cancer - recurrence - tumor marker - human epididymis protein 4

Asian Pac J Cancer Prev, **17 (9)**, 4483-4486

Introduction

Ovarian cancer is one of the most common gynecologic cancers all over the world. The estimated annual incidence is 225,500 cases worldwide, and 140,200 patients die every year from the disease(United States Cancer Statistics, 1999). It is the sixth most common cancer in female of Thailand with the age-standardized incidence rate (ASR) of 6.0 per 100,000 populations (Wilailak et al., 2009; Imsamran et al., 2015). and ranks the highest cause of death among female cancer (Narakorn et al., 2011).

Though ovarian cancer can be curable in early-diagnosed cases where the disease is limited to the ovary, however most patients are diagnosed when at more advanced stages (International Federation of Obstetrics and Gynecology [FIGO] stage III-IV) (Narakorn et al., 2011).

However, increasing rate of earlier diagnosis for ovarian cancer has remain difficult due to the relative dearth of associated symptoms and lack of specific serum biomarker.

Currently used as a diagnostic marker for ovarian cancer, cancer antigen 125 (CA-125) is elevated in roughly 80% of patients with ovarian cancer and 30% of patients with other primary cancers with extensive intra-abdominal disease. Accordingly, serum CA-125 levels are not only elevated in ovarian malignancies, but also benign ovarian diseases as well as any other inflammatory conditions of the peritoneum, pleura and pericardium (Drapkin et al., 2005; Li et al., 2009). Moreover, as CA-125 levels are elevated in less than half of cases of early stage ovarian cancer (Berek et al., 2007), a new biomarker for ovarian cancer is clearly needed. First identified in the epithelium of the distal epididymis, human epididymis protein 4

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(HE4) was originally believed to represent a protease inhibitor for sperm maturation and contribute to intrinsic immunity. HE4 is also one of 14 homologous genes on chromosome 20q12-13.1 that encodes proteins with a whey acidic protein-type four disulphide core domain(Lin Y et al., 2005). Emerging data now suggests that serum levels of HE4 is elevated in ovarian cancer patients, demonstrating similar sensitivity and increased specificity for ovarian cancer when compared with CA-125 (Moore et al., 2008). HE4 is also elevated in lung adenocarcinoma, transitional cell, breast, renal and pancreatic carcinomas (Anastasi et al., 2010).

The recent study (Plotti et al., 2012). suggest a possible role for serum HE4 as a diagnostic marker for detecting ovarian cancer. Serum HE4 levels were significantly higher in the ovarian cancer group when compared with patients with other benign ovarian tumors ($P<0.05$), and showed comparable sensitivities in detecting ovarian cancer to CA-125.Serum HE4 levels may not only allow for the detection of ovarian cancer, but also allow for better differentiation of cases of ovarian cancer versus other benign ovarian tumors compared with serum CA-125 (Trudel et al., 2010).

HE4 levels and the Risk of Ovarian Malignancy Algorithm (ROMA) have recently been shown to improve the sensitivity and specificity of epithelial ovarian cancer (EOC) diagnosis. Measurement of combined HE4 and CA125 levels provides a more accurate method for EOC diagnosis.

Materials and Methods

This prospective cohort study was approved by the ethical committee of Sunpasittiprasong Hospital.

Population and Sample

1. Target population: The target population was the EOC patients who were cured at Sunpasitthiprasong hospital from June 2014 to March 2016. The patients were operated by surgical staging. After that, the patients were treated by chemotherapy by paclitaxel and carboplatin formula every three weeks for six cycles. After taking completed treatment, then took monitoring of HE4 and CA125 results for one month. Then it was monitored every three months until the end of the research.

2. Inclusion criteria: Every case of patients who were proved that being an epithelial ovarian cancer FIGO stage III-IV. They had been complete treatment by surgery and adjuvant chemotherapy six cycles from June 2014 to March 2016. Also, they must make consent to participate in the study.

3. Exclusion criteria: The patients who had been diagnosed that being an epithelial ovarian cancer but refused to participate in the study.

Monitoring and Data collection

This prospective cohort study was approved by the ethical committee of Sunpasittiprasong Hospital. The inclusion population were those common EOC FIGO stage III-IV who were diagnosed and treated at Sunpasittiprasong Hospital during June 2014 to March 2016. Those who refused were excluded from the study. The diagnosis were done by gynecologic oncologists with physical examination, abdominal ultrasonography, chest and abdominal X-rays and CT scan or MRI in some selected patients. Surgical exploratory laparotomy with cytoreductive surgery were done with complete or incomplete resection.

The patients were followed up every month after completion of chemotherapy courses with routine physical examination, chest or abdominal X-rays, CT scan , MRI or chest, abdomen or pelvic cavity, . In biomarker with CA-125 and HE4 levels less than doubled from post-operative biomarker defined as "non-rising" while those who had CA-125 and HE4 increase two fold from post-operative biomarker were defined as "rising".

Statistical analysis were descriptive, bivariate analysis and logistic regression using stata version 13 package. The logistic regression statistics used in forecasting of HE4, checking for a tumor marker in forecasting a recurrence of epithelial ovarian cancer. Then line graph of receiver operating characteristic (ROC) was used in comparison of CA125 and HE4 to compare the difference effective indicator of recurrent of the disease.

Results

The results on studying 47 patients, who were operated, chemotherapy and complete response for 22 months from June 2014 to March 2016 were shown in Figure 1.

1). The age that most found epithelial ovarian cancer was 51-60 years, 24 cases.

2). The age that most found epithelial ovarian cancer recurrence was 51-60 years, 10 cases.

All of the research conduction period, the participants were dead of five cases. The kind of EOC, divided by world health organization 1973 (Berek et al., 2007), as follows, serous, mucinous, endometrioid, clear cell, transitional cell tumors (Brenner tumors) mixed epithelial undifferentiated, and unclassified. Figure 2 shows all of the participants were classified by cell type

The highest found case of EOC was serous carcinoma, that was 20 cases (47.5%). Moreover, it could be founded endometrioid carcinoma 13 persons (34%), mucinous carcinoma 6 cases (12.7%), clear cell carcinoma 3 cases (6.3%), and Brenner tumor 1 case (2.1%).

The highest recurrent cases were serous carcinoma of

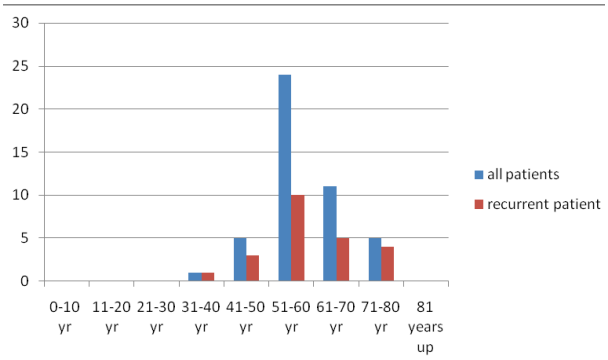

Figure 1. Ages of Participants and Recurrences of Epithelial Ovarian Cancer

10 cases (43.4%). Furthermore, endometrioid carcinoma 6 cases (26%), mucinous carcinoma 4 cases (17.3%), clear cell carcinoma 2 cases (8.6%), and Brenner tumor 1 case (4.3%).

The results of monitoring of the epithelial ovarian cancer cases who were operated, chemotherapy, until complete response from January 2015 to March 2016 at Sunpasitthiprasong hospital as shown in Figure 3. Figure 3 shows the patients with recurrent epithelial ovarian cancer, classified by cell type. The highest recurrent cases were 23 cases (48.9%) out of 47 participants. The use of tumor marker HE4 for the cases monitoring found that:

1). The recurrent cases, who had increasing of HE4 were in 21 cases (91.3%).

2). The recurrent cases, who had normal of HE4 were in 2 cases (8.7%).

Furthermore, Figure 3 shows recurrent cases of 9 (39.1%), having HE4 more than normal rate, but CA125 were normal. The recurrent case who had normal HE4 and CA125 was in 1 case (4.3%). The recurrent cases who had HE4 more than normal were 2 cases (8.3%). The non-recurrent case, who had HE4 and CA125 more than normal was in 1 (4.1%).

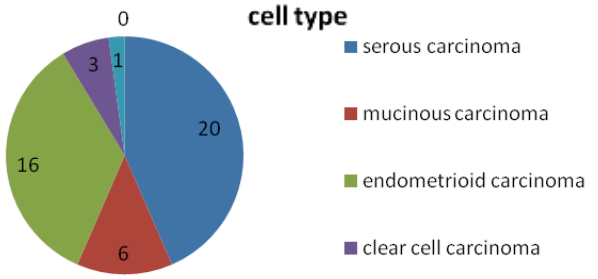

Figure 2. Histology of the Tumours

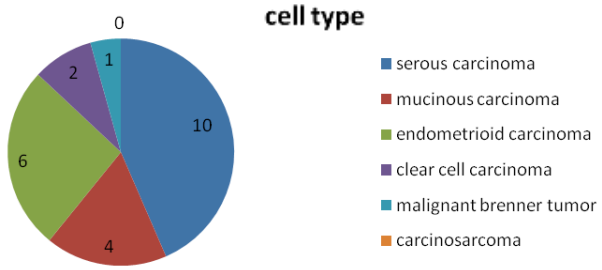

Figure 3. Histology of Recurrent Epithelial Ovarian Cancer

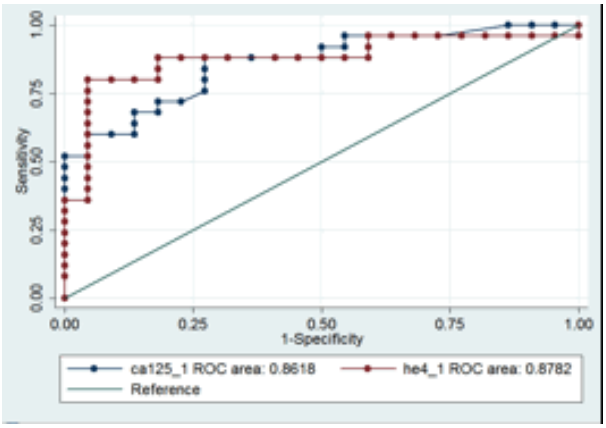

Figure 4. ROC Curves of CA125 and HE4 in Recurrent Epithelial Ovarian Cancers

Table 1. Comparison of HE4 in the Diagnosis of Recurrent Epithelial Ovarian Cancer

HE4 \ Disease	Recurrenct	Non-recurrent
rising	21	3
Non rising	2	21

Table 2. Comparison of CA 125 in the Diagnosis of Recurrent Epithelial Ovarian Cancer

CA 125 \ Disease	Recurrenct	Non recurrent
rising	12	2
Non rising	11	22

Table 3. Comparision of HE4 and CA125

Statistical analysis	HE4 (%)	CA 125 (%)
Sensitivity	91.3	52.2
Specificity	87.5	91.7
Positive predictive value	87.5	85.7
False positive	12.5	14.3
False negative	8.7	47.8

Table 1 showed that HE4 had sensitivity of 91.3%, specificity of 87.5%,positive predictive value of 87.5%, false positive 12.5% and false negative 8.7%. The results of monitoring on epithelial ovarian cancer patients by co-using tumor marker CA125 showed as follows.

1). The recurrent were found increasing of CA125 value in 12 cases (52.2%).

2). The recurrent cases, who had CA125 at normal level in 11 cases (47.8%).

Table 2 showed that CA125 had sensitivity 52.17%, specificity 95.6%, and positive predictive value 85.7%,false positive 14.3% and false negative 47.8%.

Table 3 In comparision of HE4 and CA125.The sensitivity of HE4 in detecting recurrent EOC is far more statisfied than CA125 of the sensitivity of 91.3% and 52.2% with a stastical significant (p-value 0.022) specificity of HE4 87.5% and 91.7% of CA125 .False negative of HE4 was 8.7% and CA125 was 47.8%.

Forecast hypothesis

1. HE4 could forecast the recurrent of epithelial ovarian cancer patients in the treatment and monitoring cases.

Variable	B	S.E.	Wald	df	p-value	Exp(B)
HE4	0.018	0.008	5.213	1	0.02242	1.019
Constant	-1.926	0.761	6.411	1	0.01134	0.146

The table showed that HE4 could forecast the recurrence of epithelial ovarian cancer cases statistically significant (p-value=0.02242) and could be written as regression equation as follows.

$$Z=-1.926+0.018\ (HE4)$$

2.HE4 could forecast the recurrence of epithelial ovarian cancer cases better than the previous method using CA 125. The cancer manifestations, CA 125 had under a curve area at 0.8618 (95%, CI= 0.76885-0.98751). By comparison of the both of under curve areas by statistical

hypothesis found that CA125 and HE4 were not different effective in detecting the recurrent cases (p-value=0.8314) as shown in Figure 4.

Discussion

The study of human epididymis protein 4 (HE4) to forecast the recurrences of epithelial ovarian cancer cases for 22 months, showed that the highest rate occurrence of the diseases was at the age of 51-60 years. Serous carcinoma was the highest recurrent diseases. The total participants were 47 cases. The recurrent cases were 23 cases (48.9%), in accordance with the study of Govindan (Govindan et al., 2012) which revealed that the recurrent cases were found at 44% (2 years survival rate in stage III and IV). Following of treatment by using tumor marker HE4 could forecast the recurrent cases and was better sensitivity than CA125 (91.3% *VS* 52.7%). However, comparison of the effectiveness of HE4 and CA125 on forecasting the recurrent cases was not different (p value=0.8314) but the increased HE4 could detect the recurrent cases faster than CA125 for 3-6 months. The study was in accordance with Anastasiasi (Anastasi et al., 2010), who studied HE4 as a new potential early biomarker for the recurrence of ovarian cancer, which found that HE4 had sensitivity of 96.9%, but CA125 had sensitivity of 85.7%. In addition, the higher HE4 could detect recurrence of ovarian cancer faster than CA125 for 5-8 months.

The limitation of the study was the period of time of curing and patients monitoring, due to the researcher had 3 years for studying as the house physician. The suggestion was that providing more time for the study, the amount of recurrent cases maybe much more than this current study's patient amount.

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