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Original Article

Oncology Section

Serum HE4 Detects Ovarian Cancer Recurrence Earlier Than CA 125: Indian Study

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ABSTRACT

Introduction: Recurrence is a frequent phenomenon of the natural history of epithelial Ovarian Cancer (OC). Early detection of recurrence is important. Clinical examination combined with Carbohydrate Antigen 125 (CA125) and imaging are used for the follow-up of these patients. Human Epididymis Protein 4 (HE4) is a recent marker which is found to have elevated in OC.

Aim: To study the role of HE4 in detection of OC recurrence.

Materials and Methods: This prospective study was conducted at Department of Surgical Oncology, King George's Medical University, Lucknow, Uttar Pradesh, India. Patients were enrolled from January 2014 to January 2016 after informed written consent. Total 65 patients of carcinoma ovary were prospectively followed up after completion of their primary treatment. 19 patients had clinical evidence of recurrence as detected by radiological imaging and subsequently proved by pathological examination. Timing and levels of rise in tumour marker were studied and correlated with timing of clinical evidence of disease.

Results: HE4 and CA125 detected recurrence in 19 (100%) and 14 (73.7%) patients respectively. Among these 5 (26.3%) recurrence were detected by HE4 alone. In 10 (52.6%) patients, simultaneous rise in both of these markers were noticed and in 4 (21.1%) patients HE4 started rising before CA125 with a lead time of 3.25 months. CA125 was found to be in normal range in all mucinous carcinoma and two out of 16 serous carcinoma.

Conclusion: HE4 is a potential useful serum marker to detect OC recurrence timely and better as compared to traditional utilised CA125. Future studies based on recurrence detection by HE4 may provide evidence on its role on survival.

Keywords: Carbohydrate antigen 125, Carcinoma ovary, Early detection, Human epididymis protein 4

INTRODUCTION

Ovarian Cancer (OC) is the leading cause of death from gynaecologic malignancy among women across the world. India constitutes approximately 10% of global burden of this disease [1]. Despite an aggressive upfront treatment strategy (surgery plus chemotherapy), leading to clinical remission in more than 80% of patients, the relapse free survival varies from 95.8% {for early International Federation of Gynaecology and Obstetrics (FIGO) stages} to 33.6% (for advanced stages) at two years [2]. At present, periodical evaluation of CA125 combined with physical examination and/or imaging is the recommended strategy for OC follow-up, typically every three to four months in the first one to two years after primary treatment and then every six months until the fifth year [3].

The current challenge is to try to anticipate the diagnosis of OC recurrence and to translate this early diagnosis of relapse in a survival improvement. New biomarkers are being tested in the follow-up of patients with OC to improve the follow-up program performance. HE4 is one such marker, which is over expressed, in OC. HE4 belongs to the family of Whey Acidic Four Disulfide Core (WFDC) proteins [4]. It was reported to be expressed in a number of normal tissues including epithelium of respiratory and reproductive tissues [5]. In addition to expression on a cellular level, secreted HE4 was detected in high levels in the serum of OC patients [6]. Recent data shows the promising role of HE4 in early detection of OC recurrence [7]. We aimed to study the role of HE4 in detection of the OC recurrence.

MATERIALS AND METHODS

This prospective study was conducted at Department of Surgical Oncology, King George's Medical University, Lucknow, Uttar Pradesh, India. Patients were enrolled from January 2014 to January 2016 after informed written consent. We included those patients of epithelial ovarian carcinomas who were in regular follow-up after prior complete treatment but presented with recurrence during the period of the present study.

Clinical examination, serum CA125 levels and radiological imaging such as Ultrasonography (USG) and/or Computed Tomography (CT scan) of whole abdomen were used to follow-up these patients at the present institution as a standard protocol. Serum HE4 levels were measured in addition for the present study.

The recurrence was confirmed pathologically in all cases. Timing and levels of rise in tumour marker were studied and correlated with timing of structural evidence of disease. All procedures performed in present study involving human participants were in accordance with the ethical standards of the institutional/national research committee and with the Helsinki declaration of 1975 that was revised in 2000. All data were entered electronically in SPSS software (version 20.0). Continuous data were summarised as mean±Standard Error (SE) of the mean while discrete (categorical) data in numbers and percentages.

RESULTS

A total of 65 patients were followed up of which 19 patients had recurrent disease. All patients had positive histology/cytology of recurrences. The clinical and pathological characteristics of these patients are summarised in [Table/Fig-1]. The age of patients ranged from 35-55 years with mean age of 45.58 years. All 19 patients with recurrent disease had advanced (FIGO III and IV) stage disease at the time of primary diagnosis. All of them underwent six to eight cycles of paclitaxel and carboplatin combination chemotherapy either in sequential manner after primary debulking surgery or as three to four cycles of Neoadjuvant Chemotherapy (NACT) followed by interval debulking and remaining adjuvant chemotherapy. Among

these patients, mostly had FIGO stage III (78.9%) and serous histology (84.2%). Majority of these presented at the time of first recurrence (78.9%). Recurrent disease was found outside the pelvis either in the abdomen or pleural cavity. The median follow-up of patients was 18 months. The median Disease Free Interval (DFI) of patients was 18 months.

Among 19 patients, both HE4 and CA125 rose simultaneously in 10 patients, which included one patient in whom both biomarkers were elevated six months prior to clinical recurrence. In five patients, HE4 elevation alone was detected at the time of recurrence. Though, in remaining four patients both markers elevated before clinical recurrence, but in all of them HE4 elevated before CA125 with mean lead time of 3.25 months. Overall, HE4 was elevated at or before clinical evidence of recurrence in all 19 patients who had recurrence. In comparison, CA125 was elevated in 14 (73.7%) patients at or before clinical evidence of recurrence. Rest 26.3% patients had normal CA125 levels at the time of recurrence. All patients in whom simultaneous elevations of both the markers were observed and those in whom HE4 elevation prior to CA125 was found had serous histology. Among five patients in whom HE4 alone was elevated at the time of clinical recurrence, three had mucinous histology, while two had serous histology [Table/Fig-2]. The values of both biomarkers at the time of recurrence are shown in [Table/Fig-3].

Clinical characteristics	Patients (n=19) (%)
Age (years)	
Mean±SE, median	45.58±1.27, 46
Min-Max	35-55
FIGO stage	
III	15 (78.9%)
IV	4 (21.1%)
Histology	
Serous	16 (84.2%)
Mucinous	3 (15.8%)
Recurrences (no)	
1	15 (78.9%)
2	4 (21.1%)
Recurrences (site) ascites	
Present	11 (57.9%)
Absent	8 (42.1%)
Peritoneal/omental	
Present	15 (78.9%)
Absent	4 (21.1%)
Retroperitoneal lymph nodes	
Present	3 (15.8%)
Absent	16 (84.2%)
Pleural effusion	
Present	5 (26.3%)
Absent	14 (73.7%)
Disease free interval (months)	
Mean±SE, median	20.79±2.52, 18
Min-Max	6-48

[Table/Fig-1]: Distributions of clinical and pathological characteristics of patients with recurrent disease.
SE: Standard error

Rise in level of markers (CA125 and/or HE4)	Patients (n=19) (%)	Histological subtypes	Patients (n=19) (%)
Simultaneous	10 (52.6%)	Serous	10 (52.6%)
		Mucinous	0 (0.0%)
HE4 alone	5 (26.3%)	Serous	2 (10.5%)
		Mucinous	3 (15.8%)
HE4 prior to CA125	4 (21.1%)	Serous	4 (21.1%)
		Mucinous	0 (0.0%)
CA125 prior to HE4	0 (0.0%)	None	0 (0.0%)
CA125 alone	0 (0.0%)	None	0 (0.0%)

[Table/Fig-2]: Distribution of patients according to rise in levels of CA125 and HE4.

Test parameters	Statistics
CA125 (U/mL)	
Mean±SE, median	652.94±186.08, 112
Min-Max	5.50-2670.10
HE4 (pmol/L)	
Mean±SE, median	418.85±61.17, 273
Min-Max	162.00-928.50

[Table/Fig-3]: Values of CA125 and HE4 at the time of recurrence.
SE: Standard error

DISCUSSION

OC management has been a challenge to the oncologist from the past to the present time. Despite aggressive surgical attempt to debulk the disease and modern combination chemotherapy, the disease remission is temporary. The unfortunate diseased females eventually suffer from multiple recurrences. Moreover, in majority of the cases disease free interval gets shorter and shorter with every recurrence. The recurrence is rather a rule than exception in females diagnosed with this disease especially at advance stages.

Schummer M et al., found 20 recurrences out of 23 patients with a median progression free interval of 18 months (9-48 months). Among these 20 patients, HE4 and CA125 were elevated in 70% and 60% respectively. In 15% patients, none of the marker was elevated. Total 25% recurrences were detected by HE4 alone and CA125 alone detected 15% recurrences. In six (30%) patients both CA125 and HE4 elevated simultaneously. Among these one (5%) patient had elevation of both the markers three month earlier than recurrence could be seen on imaging. These authors had used CA125 threshold of 38 U/mL in all patients, while HE4 threshold were 44 pmol/L in premenopausal and 62 pmol/L in postmenopausal females [8].

Havrilesky LJ et al., studied, HE4, glycodelin, MMP7 and CA125 for detection of disease recurrence. Of 27 patients who experienced recurrence of OC, sensitivity for predicting recurrence was 100% for the biomarker panel and 96% for CA125. At least one of the panel biomarkers was elevated earlier (range 6-69 weeks) than CA125 and prior to clinical evidence of recurrence in 14 out of 27 (52%) patients. They found lead time for HE4 and MMP7 over CA125 that was 1-15 months [9].

In another study, CA125 and HE4 levels were measured as indicator of the recurrence of the disease in eight patients followed up for 20 months after OC diagnosis. The follow-up study showed an increase of HE4 five to eight months before CA125 increment in five out of the eight patients [2].

Allard J et al., found HE4 to compare well to CA125 for recurrence detection, including patients where CA125 is not of utility [10]. Manganaro L et al., retrospectively investigated two biomarkers, CA125 and HE4, as indicator of relapse in epithelial OC patients with recurrent disease in combination with CECT findings. During their study period they found nine out of 21 patients with disease recurrence. They concluded that, in case of disease recurrence, increased levels of HE4 may precede an elevation in CA125 by approximately three months. Moreover, HE4 serum levels combined with CECT imaging may improve the management of women affected by OC [11].

The ability of HE4 to predict OC recurrence earlier than CA125 has been shown in a recent systematic review of seven studies. The

authors of this study concluded that more studies are needed to validate the role of HE4 in early detection of OC recurrence [7].

The present study includes 19 patients with recurrent epithelial ovarian carcinoma with median DFI of 20.8 months (6-48 months). HE4 and CA125 detected recurrence in 100% and 73.7% patients respectively. Among these 26.3% recurrence were detected by HE4 alone. In 52.6% patients simultaneous rise in both of these markers were noticed and in 21.1% patients HE4 started rising before CA125 with a lead time of 3.25 months. CA125 was found to be in normal range in all mucinous carcinoma and two out of 16 serous carcinoma.

In EORTC 55955 collaborative trial women with OC in complete remission after first line platinum based chemotherapy and a normal CA125 concentration were registered. Benefits of early treatment on the basis of increased serum CA125 concentrations were compared with delayed treatment on the basis of clinical recurrence. Result of the trial showed no evidence of a survival benefit with early treatment of relapse on the basis of a raised CA125 concentration alone [12]. Results of this trial are often criticised because of two reasons. Firstly, CA125 levels are not raised in all cases of recurrent OC on follow-up. And secondly, the lead time with CA125 level is not good enough to show a survival difference when these patients were retreated solely on the basis of rising CA125. Therefore, a much sensitive marker for the disease recurrence may potentially change the management of this disease and confer a long term disease free and overall survival to the patients. Serum HE4 data looks promising in this regard.

LIMITATION

Limitation of the present study is small sample size. Another limitation is that we do not have baseline levels of HE4 of all patients at the time of primary resection, tending to have bias towards sensitivity and specificity for predictability by both HE4 and CA125. Still, present study provides essential information regarding predictive and possibly a prognostic value of HE4 in recurrent OC. These findings of our study need to be validated in the larger cohort of patients.

CONCLUSION

HE4 is a potential useful serum marker to detect OC recurrence timely and better as compared to traditional utilised CA125. Early detection provides an opportunity to plan treatment, counseling of patient and family. Future studies based on recurrence detection by HE4 may provide evidence on its role on survival.

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REFERENCES

[1] Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 10/11/2015.
[2] Anastasi E, Marchei GG, Viggiani V, Gennarini G, Luigi F, Reale MG. HE4: a new potential early biomarker for the recurrence of ovarian cancer. Tumour Biol. 2010;31:113-19.
[3] Morgan RJ Jr, Alvarez RD, Armstrong DK, Burger RA, Chen L, Copeland L, et al. Ovarian cancer, version 2.2013. J Natl Compr Canc Netw. 2013;11:1199-209.
[4] Bouchard D, Morisset D, Bourbonnais Y, Tremblay GM. Proteins with whey-acidic-protein motifs and cancer. Lancet Oncol. 2006;7:167-74.
[5] Galgano MT, Hampton GM, Frierson HF Jr. Comprehensive analysis of HE4 expression in normal and malignant human tissues. Mod Pathol. 2006;19:847-53.
[6] Hellstrom I, Raycraft J, Hayden-Ledbetter M, Ledbetter JA, Schummer M, McIntosh M, et al. The HE4 (WFDC2) protein is a biomarker for ovarian cancer. Cancer Res. 2003;63:3695-700.
[7] Capriglione S, Luvero D, Plotti F, Terranova C, Montera R, Scaletta G, et al. Ovarian cancer recurrence and early detection: may HE4 play a key role in this open challenge? A systematic review of literature. Med Oncol. 2017;34:164.
[8] Schummer M, Drescher C, Forrest R, Gough S, Thorpe J, Hellström I, et al. Evaluation of ovarian cancer remission markers HE4, MMP7 and Mesothelin by comparison to the established marker CA-125. Gynecol Oncol. 2012;125:65-69.
[9] Havrilesky LJ, Whitehead CM, Rubatt JM, Cheek RL, Groelke J, et al. Evaluation of biomarker panels for early stage ovarian cancer detection and monitoring for disease recurrence. Gynecol Oncol. 2008;110:374-82.
[10] Allard J, Somers E, Theil R, Moore RG. Use of a novel biomarker HE4 for monitoring patients with epithelial ovarian cancer. J Clin Oncol (Meeting Abstracts). 2008;26:5535-35.
[11] Manganaro L, Michienzi S, Vinci V, Falzarano R, Saldari M, Granato T, et al. Serum HE4 levels combined with CECT imaging improve the management of monitoring women affected by epithelial ovarian cancer. Oncol Rep. 2013;30:2481-87.
[12] Rustin GJ, van der Burg ME, Griffin CL, Guthrie D, Lamont A, Jayson GC. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial. Lancet. 2010;376:1155-63.

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