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Original Article

Usefulness of Serum HE4 in Monitoring Chemotherapy Response During Neoadjuvant Chemotherapy in Advanced Epithelial Ovarian Carcinoma

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Abstract

Background: Ovarian cancer (OC) is the most lethal gynecological cancer, being the eighth leading cause of cancer death in women. Fifty to seventy percent of treated patients will experience a relapse associated with chemoresistance. This is one of the major challenges to deal with in ovarian cancer management.

Objectives: This survey was driven to evaluate the effectiveness of serum HE4 in monitoring the response of chemotherapy in advanced epithelial ovarian cancer who are selected for Neoadjuvant Chemotherapy (NACT).

Methods: This cross-sectional study was conducted from January 2022 to December 2022 at the National Institute of Cancer Research and Hospital to find out the association of serum levels of HE4 with the clinical and tomographic response after neoadjuvant chemotherapy in advanced ovarian carcinoma.

Results: Mean age of the respondents was 52.27 (SD: ±10.55) years. Leading number of patients were from the 41-50 years age group. Association between response category and HE4 level after NACT is examined in the current study. The mean value of HE4 after NACT in no-response group was 539.03 whereas in response group this value decreased to 140.58. On independent t-test this difference was statistically significant (p=0.027).

Conclusion: HE4 biomarker can be effectively used to monitor the response of chemotherapy in advanced epithelial ovarian cancer, Further study is needed to understand the impact of the biomarkers in terms of successful cytoreduction, in predicting platinum sensitivity, disease-free survival, risk to progress and overall survival.

Key Words: Advanced Epithelial Ovarian Carcinoma, Neoadjuvant Chemotherapy, Serum HE4.

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Introduction

Ovarian cancer is the seventh most common cancer among women and a leading cause of death in women with gynaecological malignancies. Globally, there are 313959 new cases per year, with 207252 deaths per year.[1] Almost 80% of cases are diagnosed as advanced stage disease.[2] Current treatment for advanced epithelial ovarian cancer (AOEC) involves primary debulking surgery followed by an adjuvant chemotherapy regimen based on the combination of platinum and taxane, or the initial administration of neoadjuvant chemotherapy (NACT) followed by surgery.[2]

Neoadjuvant chemotherapy followed by surgery has been proposed to result in the same clinical outcome as primary surgery in combination with postoperative chemotherapy when complete initial debulking is not deemed to be possible.[3]

Management of ovarian cancer has improved over the last

three decades, with an increase in 5-year survival from 38 to 46%, related to the more consistent use of cytoreductive surgery and combination chemotherapy with platinum compounds and taxanes[1]. Despite the improvement in overall survival, a fraction of patients with advanced stage disease fail to respond to primary therapy and at least 70% relapse[4]. Many women will have an excellent response to primary treatment.

With successful treatment options it has become increasingly important to have accurate methods of assessing response to treatment, especially in patients undergoing neoadjuvant chemotherapy prior to surgery and for detecting recurrent disease in patients on maintenance therapy. Earlier detection of progressive or recurrent disease is important as the discontinuation of maintenance therapy at the first signs of progression can reduce cumulative toxicities and cost[5]. Tumor Biomarkers such as CA125, HE4 have been used to monitor response to treatment and to detect recurrence[4].

HE4 (human epididymis protein 4) is a protease inhibitor. HE4 has been approved by the Food and Drug Administration (FDA) to monitor disease progression of epithelial ovarian cancer[4]. Up to now, the most promising new indicator seems to be (HE4). Consequently, HE4 has emerged as an important biomarker that complements CA 125 in discriminating between benign and malignant pelvic masses, monitoring response to treatment and detecting recurrences of ovarian cancer[7].

In this study, the aim was to observe the association of serum levels of HE4 before and after NACT with tomographic image after NACT and thereby to evaluate the effectiveness of this biomarker in monitoring the chemotherapy response in advanced epithelial ovarian carcinoma. Nowadays, non-invasive methods for early identification of ovarian cancer treatment response, are needed and there is growing interest in the evaluation of the role of serum biomarkers.

Some studies showed HE4 has a more rapid decrease rate during chemotherapy than CA-125, and re-detected faster than CA-125 in patients who did not have a good chemotherapy response.

Up to date this issue is still debating on which criteria should be used to see the chemotherapy response in epithelial ovarian cancer. Advanced imaging needed for the use of RECIST criteria that is a established method for monitoring the chemotherapy response. Its measurement is critical and expert interpreters dependent.

In addition it is expensive and has radiation hazards. On the other hand, serum HE4 is serological test, which are patients friendly, no radiation hazards, easy to interpret and less expensive.

So, if the association is established by this study result, it may be better predictor to see the chemotherapy treatment response. Therefore, it would be rational to study the utility of HE4 in monitoring the response of chemotherapy during treatment.[3]

Methodology

This prospective observational study was conducted during January 2022 to December 2022 in department of Gynaecological Oncology, National Institute of Cancer Research & Hospital, Mohakhali, Dhaka. Purposive sampling technique was applied where the study populations were 30 diagnosed cases as advanced epithelial ovarian cancer attending Gynaecological Oncology department of National Institute of Cancer Research and Hospital and were planned to get NACT. Those patients who were medically unfit for upfront surgery, who had comorbidity that would interfere to surgery, patients with hard fixed mass, with large pleural effusion, huge ascities, parenchymal liver or lung metastasis were selected for NACT. Initially all patients were evaluated thoroughly by detailed history, clinical examination and advanced imaging. After taking informed concent HE4 levels were estimated in patients meeting inclusion criteria. Then the patients were referred to Medical Oncology Department for neoadjuvant chemotherapy. After 3-4 cycles of chemotherapy all patients were again evaluated thoroughly by detailed history, clinical examination and advanced imaging. HE4 was performed within three to four weeks after completion of chemotherapy. Finally comparative analyses of HE4 level was done with clinical & tomographic response. Pre-designed sheet was used to collect socio demographic data, examination findings and

investigation findings. Checklist was used to keep record of the examination and investigation findings.

Prior to the commencement of the study, the protocol was approved by the Ethics Committee of NICRH. The aims & objectives of the study were explained to respondents & informed written consent was taken from each subject or from their legal guardians. They were assured that all information & records would be kept confidential and be used for research purposes only. It was made clear to them that they were free to take part or withdraw from any part of the study at any stage. Refusal to take part or withdrawal from the study would not hamper their treatment.

Data were collected, coded, revised and entered using the SPSS for Windows software (IBM SPSS Statistics for Windows, version 25.0, Armonk, NY, IBM Corp.). The qualitative data were presented as number and percentages while the quantitative data were presented as mean, standard deviation and ranges. For analysis of quantitative data paired and independent sample t-tests were used. The significance level was set at 5%.

Results

This prospective observationl study was done to evaluate the effectiveness of serum HE4 in monitoring the response of chemotherapy in advanced epithelial ovarian cancer who are selected for NACT. For this purpose, 30 patients of advanced epithelial ovarian cancer attending at Gynaecology Oncology department of NICRH were enrolled. The responses recorded in the data collecting sheets were analyzed and have been presented in the form of tables and charts with necessary description according to the objectives of the study. The findings derived from the data analysis are given below:

Table I: Socio-demographic characteristics of study participants

Socio-demographic variables	Frequency	Percentage
Age group		
<=30	01	3.3
31-50	15	50.0
>50	14	46.7
Mean (±SD)	52.27 (10.55) years	
Occupation		
Housewife	21	70.0
Service and other	09	30.0

Socio-demographic characteristics of the patients are presented in the above table (Table I). Mean age of the respondents was 52.27 (SD: ±10.55) years. Leading number of patients were from the 31-50 years age group. Seventy percent of the respondents were homemakers and only nine patients had some occupation mainly service.

Table II: Personal characteristics of the patients

Variables	Frequency	Percentage
Menstrual status		
Pre-menopausal	10	33.3
Post-menopausal	20	66.7
Marital status		
Married	26	86.7
Widow	04	13.3
Parity		
Multipara	25	83.3
Grand multipara	05	16.7
Use of contraception		
Yes	20	66.7
No	10	33.3

Personal characteristics of the patients are presented in the above table (Table II). Two-third of the respondents were in post-menopausal state at the time of data collection. Around 87% were married. Twenty-five respondents were multipara, i.e., gave birth to 2-4 four children. Exactly two-third gave history of OCP use.

Table III: General characteristics of the participants before NACT

Variables	Frequency	Percentage
Anaemia		
Mild	18	60.0
Moderate	11	36.7
Severe	1	3.3
Oedema		
Present	7	23.3
Absent	23	76.7
Lymph node		
Palpable	2	6.7
Not palpable	28	93.3
BMI	22.54(±2.40) Kg/m^2	

NACT= Neo-adjuvant chemotherapy

General characteristics before NACT are presented in the Table III. Sixty percent of the respondents experienced mild form of anaemia while 11 patients had moderate anaemia. Only one patient had severe form of anaemia. Before chemotherapy only seven patients (23.3%) reported to have oedema and two patients (6.7%) had palpable lymph nodes. Mean BMI before NACT was 22.54 (±2.40) Kg/m^2.

Table IV: Clinical findings of participants before NACT

Variables	Frequency	Percentage
Per abdominal tumour size		
<10 cm	15	50.0
> 10 cm	15	50.0
Bimanual tumour size		
<10 cm	15	50.0
> 10 cm	15	50.0
Rectovaginal exam finding		
Nodule in POD present	7	23.3
Nodule in POD absent	23	76.7

POD= Pouch of Douglas

Some clinical findings before NACT are given in the Table IV. On per abdominal examination 15 (50%) patients had <10 cm tumour size and equal numbers of patients had >10 cm tumour. The same results were revealed on bimanual examination. On rectovaginal examination seven (23.3%) had nodule in pouch of Douglas.

Table V: Computed Tomography (CT) scan findings of abdomen before NACT

Variables	Frequency	Percentage
Ascites		
Absent	2	6.7
Mild	3	10.0
Moderate	13	43.3
Huge	12	40.0
Number of tumuor		
1	24	80.0
2	6	20.0
Lymph node involvement		
Involved	2	6.7
Not involved	28	93.3
Metastasis		
Present	16	53.3
Absent	14	46.7

CT scan findings before NACT are given in the above table (Table V). Before giving NACT moderate (43.3%) to huge (40%) ascites were present. There were single tumours in 24 cases (80%) and double tumours in six patients (20%). In most of the cases (93.3%) lymph nodes were not involved. Metastasis was present in majority of the cases (16/30) (53.3%).

Table VI: General characteristics of the participants after NACT

Variables	Frequency	Percentage
Anaemia		
Mild	29	96.7
Moderate	1	3.3
Jaundice		
Present	1	3.3
Absent	29	96.7
Oedema		
Present	6	20.0
Ab sent	24	80.0
Lymph node		
Palpable	3	10.0
Not palpable	27	90.0

General characteristics after NACT are presented in the Table VI. Most of the respondents (96.7%) had only mild form of anaemia. Only one patient had developed jaundice after NACT. After chemotherapy oedema was found in six patients (20%). In this setting three patients (10%) had palpable lymph nodes.

Table VII: Clinical findings of participants after NACT

Variables	Frequency	Percentage
Per abdominal tumour size		
<10 cm	23	76.7
> 10 cm	7	23.3
Bimanual tumour size		
<10 cm	22	73.3
> 10 cm	8	26.7
Rectovaginal exam finding		
Nodule in POD present	6	20.0
Nodule in POD absent	24	80.0

Some clinical parameters after NACT are shown in the Table VII. On per abdominal examination 23 patients (76.7%) had <10 cm tumour size and seven patients (23.3%) had >10 cm tumour. On bimanual examination 22 patients (73.3%) had <10 cm tumour size. On rectovaginal examination six (20%) had nodule in pouch of Douglas and the rest 24 patients (80%) did not have such nodule.

Table VIII: CT scan findings of abdomen after NACT

Variables	Frequency	Percentage
Ascites		
Absent	8	26.7
Mild	18	60.0
Moderate	4	13.3
Number of tumours		
1	18	60.0
2	4	13.3
No tumour	8	26.7
Lymph node involvement		
Involved	2	6.7
Not involved	28	93.3
Metastasis		
Present	11	36.7
Absent	19	63.3

CT scan findings after NACT are presented in the above table (Table VIII). After NACT in most cases (60%) mild ascites were present. Only four patient (13.3%) had moderate ascites. There were single tumours in 18 cases (60%) and double tumours in four patients (13.3%). In most of the cases (93.3%) lymph nodes were not involved. Metastasis was absent in majority of the cases (19/30) (63.3%).

Table IX: Distribution of the patients by response after NACT

Response	Frequency	Percentage
Complete response	8	26.7
Partial response	10	33.3
Progressive disease	3	10.0
Stable disease	9	30.0
Total	30	100.0

Distribution of the patients by response after NACT is presented in the above table (Table IX). Eight patients (26.7%) showed complete response. In one-third of the cases (33.3%) partial response was noted. Three patients (10%) exhibited progressive disease while in nine patients (30%) stable disease was noted.

Table X: Association between response category and HE4 level after NACT

HE4 after NACT	Mean	SD	t-test	df	*p*-value
No response	539.03	535.87	2.516	12.07	0.027 (S)
Response	140.58	144.47			

'No response' that include (Stable disease & progressive disease).
'Response' that include (complete response & partial response).
Association between response category and HE4 level after NACT is shown in the above table (Table X). The mean value of HE4 after NACT in no-response group was 539.03 whereas in response group this value decreased to 140.58. On independent t test this difference was statistically significant (p=0.027).

Table XI: Paired t-test to compare HE4 values before and after NACT

Parameter	Mean	SD	t-test	df	*p*-value
HE4 before NACT	691.250	440.505	6.361	29	<0.001 (HS)
HE4 after NACT	299.963	400.716			

HE4 values before and after NACT is shown in the above table (Table XI). Before and after NACT the mean values of HE4 were 691.3 and 299.97 respectively. On paired t-test this difference was statistically highly significant (p<0.001).

Discussion

HE4 was overexpressed in ovarian cancer. Neoplastic marker HE4 is undoubtedly one of most popular markers studied by researchers with interest in biomarkers in gynaecological oncology. Recent publications assessing the prognostic capabilities associated with this marker began to appear. To date, such reports remain scarce. This study was conducted to observe the Utility of serum HE4 in monitoring chemotherapy response during neoadjuvant chemotherapy in advanced epithelial ovarian carcinoma. Within this study 30 patients were evaluated with advanced epithelial ovarian cancer who were selected for neoadjuvant chemotherapy in the department of Gynaecological Oncology, National Institute of Cancer & Hospital, Dhaka from January 2022 to December 2022.

In this current study among 30 patients the mean age of participants was 52.27 years (SD ± 10.55) years, lower than reported globally, being 62 years[10]. Banos J A A et al.[11] in 2021 conducted a study showed the average age 57.8 years (SD ±10.3) years (86.7 %) 10. Another study conducted in India in 2019, where the median age of their participants were 46 years, which is consistent with our study[3].

Regarding personal characteristics of our study patients (In Table-II), about 66.7 % patients were post-menopausal and 33.3 % were premenopausal. Most of the patients were multipara 83.3% & about 66.7% did not use contraceptives. Lakshmanan M et al. 20193 conducted a study where most of the patients were multiparous (87.5% n = 112).

General characteristics of participants before NACT (In Table III) showed 60% of the respondents experienced mild form of anaemia while 36.7% patients had moderate anaemia and (3.3%) patients had severe form of anaemia. Our study population were examined both before and after NACT. Regarding clinical findings (In Table IV), on per abdominal examination 50% patients had <10 cm tumour size and equal numbers of patients had tumour size >10 cm. The same results were revealed on bimanual examination. On rectovaginal examination 23.3% had nodule in pouch of Douglas. After NACT 76.7% patients had <10 cm tumour size and 23.3% of patients had >10 cm tumour.

Computed tomography of abdomen (CT abdomen) before & after NACT were performed (table -V & VIII).

Before NACT huge ascites were present in 40.0% , moderate ascites 43.3% & mild ascites 10.0%. Metastasis present 53.3%.

Therapeutic response criteria of the patients after NACT in this current study (table IX) were evaluated. By tomographic standard evaluation of therapeutic response was performed according to Response Criteria in Solid Tumors (RECIST) by using t "Response" that include compete and partial response or "no response" that include stable disease and progressive disease. In this current study 26.7% patients showed complete response, 33.3% partial response, 10% exhibited progressive disease and 30% stable disease was noted. A study conducted in India showed 34% having complete response and 54% partial response[9]. Another study in India showed the therapeutic response according to RECIST criteria. Their study comprised complete response 5.5% Partial response 54.7%, Stable disease 24.2% and Progressive disease 15.62%. These were not consistent with our study, but when we calculate both complete and partial response as 'Response category this observation is similar to their study[9].

Association between response category and HE4 level after NACT is shown in this present study (table XI). The mean value of HE4 after NACT in no-response group was 539.03 whereas in response group this value decreased to 140.58. On independent t test this difference was statistically significant (p=0.027). In similar study done on Mexico showed the association of therapeutic response and HE4 level after 3rd cycle chemotherapy. P value of that study was significant (p= 0.031) which was near to similar to our result[10]. Glaz A C et al., 2018[11] conducted a study to assess the prognostic value of HE4 marker measurements at various stages of first-line chemotherapy for ovarian cancer[12]. Each patient underwent HE4 level measurements at the time of diagnosis and subsequently after the third course of adjuvant chemotherapy. The study conclude that significant effect of the normalization of the HE4 marker after therapy and 50% reduction of HE4 levels might be an independent prognostic factor of treatment response. Measurements performed during first-line treatment of ovarian cancer may have prognostic significance.

HE4 values before and after NACT were compaired by paired t test (Table XI). Before and after NACT the mean values of HE4 were 691.3 and 299.97 respectively. On paired t-test this difference was statistically highly significant (p<0.001).

Liest A L et al. 2020[12], showed in their study that the role of HE4 in monitoring chemotherapy has been evaluated regarding prognosis and prediction of platinum resistance[12]. In 86% of patients the serum levels of HE4 were under URL reported as optimally tumor reduced. The median levels of HE4 in patients with normal values at the start of chemotherapy remained below URL during treatment whereas elevated HE4 levels at start of treatment decreased significantly.

Liest AL et al. 2020[12], also suggested in their study HE4 is valid markers to monitor the response to chemotherapy, but only when the marker is above the normal range prior to start of chemotherapy[12]. Banos J A et al. in 2021[13] conducted a study to see whether CA 125 and HE4, alone or in combination were associated with therapeutic response to NACT during follow up[13]. They concluded Serum HE4 levels were independently associated with therapeutic response with advanced epithelial ovarian cancer who were treated with NACT. Potenza E et al. in 20202 conducted study regarding predictive value of combined HE4 biomarker during NACT in patients with advanced epithelial ovarian cancer[2]. They recommended HE4 for monitoring during chemotherapy, as their variation is a good prognostic factors[2].

Conclusion

The current study was done to evaluate the effectiveness of serum HE4 in monitoring the response of chemotherapy in advanced epithelial ovarian cancer who are selected for NACT. Use of HE4 level in monitoring chemotherapy response, the paired t test were similarly statistically significant. On the other hand association between tomographic response category and HE4 levels after NACT yeilded significant result ((p=0.027). Hence HE4 levels before and after NACT can be an independent biomarker to monitor the chemotherapy response during neoadjuvant chemotherapy in advanced epithelial ovarian cancer.

Ethical Clearance:

The research protocol was approved by Institutional Review Board (IRB) of National Institute of Cancer Research and Hospital (NICRH), Dhaka, Bangladesh.

Author Contributions:

1.Pervin MR: Conception and design and conducted the statistical analysis and was primarily responsible for drafting the Results and Discussion sections of the manuscript.
2.Shahana Pervin S: supervised the overall research process, contributed to the Abstract, Conclusion, and References, and reviewed the final version of the manuscript prior to submission.
3.Haque N: Guarantor accuracy and integrity of the work.
4.Ara R: Manuscript drafting and revising it critically.
5.Nila FH: Critically review of the article.
6.Talukdar MAS: contributed to the development of the Introduction and Methodology, and enhance the intellectual content of the manuscript.
7.Sarker S: Acquisition, analysis and interpretation of data.
8.Bardhan S: Preliminary manuscript drafting and revising.

Conflict of interest:

The authors declare no conflict of interest.

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