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Does a Decrease in CA-125 in Advanced Ovarian Cancer Following Neoadjuvant Chemotherapy Predict the Clinical Outcome of Patients? A Cross-sectional Study

Setareh Akhavan[1], Yalda Jefrideh[2*], Azamosadat Mousavi[3], Mitra Modares-Gilani[1], Shahrzad Sheikh-Hasani[3]

Abstract

Objectives: Although ovarian cancer is the sixth most common cancer among women, in most cases, it is not diagnosed until it covers the entire peritoneum. In the present study, it was examined the clinical outcomes of the women with epithelial ovarian cancer (EOC) in stage IIIC-IV treated with neoadjuvant chemotherapy (NACT) and its association with decreased ovarian cancer antigen (CA-125).

Materials and Methods: In this cross-sectional study, 78 women with EOC (Stage IIIC-IV) who underwent NACT at Imam Khomeini hospital, Tehran, Iran were evaluated. Demographic characteristics, aged at diagnosis, severity and stage of disease, serum CA-125 level, histological type, tumor pathology before and after chemotherapy, overall survival, and recurrence of disease was examined.

Results: In total, 78 women with mean age of 52.83 ± 10.18 (between of 29 to 77) years were evaluated. The majority of the patients had positive initial ascitic fluid cytology for malignancy (68.9%). After surgery, papillary serous was the most common histologic finding (73, 81.1%). CA-125 level post NACT (median of 25 U/mL) was significantly reduced compare to before NACT (median of 980 U/mL; $P<0.0001$), and the rate of CA-125 reduction was significantly lower in older participants' ages (r=0.274, $P=0.017$). Survival time showed a significant and strong negative correlation with the CA-125 levels before (r=-0.363, $P=0.003$) and after NACT (r=-0.383, $P=0.002$). Moreover, there was a significant negative correlation between survival time and chemotherapy courses (r=-0.363, $P=0.003$) and age (r=-0.474, $P=0.000$).

Conclusions: The results of this study showed that the clinical outcomes of patients with advanced ovarian cancer can be predicted by a decrease in serum CA-125 levels after NACT.

Keywords: Epithelial ovarian cancers, CA-125, Biomarkers, Tumor, Neoadjuvant therapy

Introduction

Epithelial ovarian cancer (EOC) is the sixth most common cancer in the world. Epithelial ovarian carcinomas make up 90% of ovarian cancers that originate from the surface layer of the ovaries or fallopian tubes (1). The malignant cells' origin is the end of the fallopian tubes, so they can infiltrate the abdominal cavity even in the primary stages when the tumor is microscopic (2). Consequently, most patients are diagnosed at the end stages when the disease has spread throughout the abdomen. These cells circulate around the abdominal cavity in lubricating fluids, such as the peritoneum, then they implant on other surfaces and progress until symptoms are revealed. Even then, symptoms such as bloating and digestive problems (often constipation) are nonspecific and easily attributed to other common benign conditions. In Europe, one-third of women with a diagnosis of EOC survive five years (3,4).

Routine treatments for ovarian cancer include surgery and subsequent chemotherapy. Surgery involves adequate staging and removing the macroscopic sites (debulking or cytoreduction) and clearance of the abdominal cavity. Given that the disease is spread in most patients, surgery is not the only treatment of the illness, and chemotherapy is needed after it (5). Chemotherapy for these patients involves treatment with platinum-containing drugs in order to kill the cancer cells that cannot be surgically removed (macroscopic disease) or are too small (microscopic disease). Chemotherapy is done before neoadjuvant surgery and in very advanced stages when the incidence of primary debulking is high (stage IIIC-IV). The next step is interval debulking surgery (IDS) (6).

The rate of neoadjuvant chemotherapy (NACT) use has been dramatically increased over the past decade. This treatment protocol is primarily used in elderly patients and people in stage IIIC-IV of cancer (7). Ovarian cancer antigen (CA-125) is often evaluated in the patients with EOC, and its serial changes over time could help to subsequent management of disease accordingly. However, interpreting the increase in CA-125 concentrations associated with tumor burden is somewhat controversial (8-10). Abu Hassan and colleagues showed that although CA-125 used as a tumor marker for monitoring the

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[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Vali -Asr Reproductive Health Research Center, Tehran University of Medical Sciences, Tehran, Iran. [2]Department of Obstetrics and Gynecology, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. [3]Department of Obstetrics and Gynecology, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
***Corresponding Author:** Yalda Jefrideh, Tel: (+98) 9166122835, Email: Drjefrideh@gmail.com

Key Messages

- The CA-125 serum levels significantly reduce after NACT in patients with advanced ovarian cancer.
- The recurrence time in patients with lower CA-125 is longer than the patients with higher CA-125.
- There is an association between serum CA125 levels and survival of patients receiving primary NACT in advanced ovarian cancer.

disease, but in terms of accuracy has limitations which showed other markers and criteria should be considered in monitoring the disease (11). Although changes in CA-125 levels after initial chemotherapy (NACT or subsequent NACT IDS) predict the prognosis of patients with EOC, the association between serum CA-125 levels after NACT and IDS is an important issue in recent studies (12-15). Therefore, the aim of this study was to investigate the serum CA-125 levels before and after NACT in patients with advanced stage of EOC and its relationship with patient cytology, survival rate, and treatment outcome.

Materials and Methods

In this cross-sectional study, the medical records of 78 women with EOC (stage IIIC-IV) who underwent NACT at Imam Khomeini hospital, Tehran, Iran from March 2012 to April 2018 were evaluated. All women with non-EOC, borderline or benign tumor, as well as the those underwent diagnostic surgery were excluded from the study.

Demographic characteristics and pathological information of participants included age at the time of diagnosis, medical history, cancer stage, tumor grade, chemotherapy courses, and CA-125 level before and after NACT were collected from the participants' medical records. Moreover, the overall survival and recurrence was evaluated. Survival time was defined as the months passed since the start of NACT and recurrence time was defined as the months passed the start of surgery to recurrence of cancer.

Data Analysis

Statistical Package for the Social Sciences (SPSS) software version 22 was used for data analysis. Data expressed as mean ± standard deviation or median (range) and/or frequency (percentage). The Wilcoxon signed rank test was used to examine the changes in CA-125 before and after NACT. The spearman correlation test was also used to determine the relationship between quantitative variables. A P value of <0.05 was considered statistically significant.

Results

The baseline characteristics of the participants and result of NACT were presented in Table 1. Before receiving NACT most of the participants (68.9%) had positive ascetic fluid cytology for malignancy, 5.6% had positive peritoneal biopsy, 3.3% had both positive ascites fluid cytology and peritoneal biopsy, 3.3% had positive omental biopsy, 3.3% had positive ovarian biopsy, and finally, 1.1% had both positive ascites fluid cytology and omental biopsy.

Table 1. Baseline Characteristics of Study Participants

Variables	
Age group (y), No. (%)	
≤50	32 (35.6%)
51-60	26 (28.9%)
≥61	20 (22.2%)
Age (y), Mean± SD	52.83 ±10.18
Gravid, Median (range)	4 (0-13)
Parity, Median (range)	4 (0-11)
Abortion, No. (%)	15 (16.7%)
Chemotherapy courses, Median (range)	3 (3-6)
Tumor Stage, No. (%)	
IIIa	5 (5.6%)
IIIb	2 (2.2%)
IIIc	67 (74.4%)
IV	3 (3.3%)
Tumor pathology (before chemotherapy), No. (%)	
Ascitic fluid cytology for malignancy	62 (68.9%)
Positive peritoneal biopsy	5 (5.6%)
Positive omental biopsy	3 (3.3%)
Positive ascites fluid cytology and omental biopsy	1 (1.1%)
Positive ascites fluid cytology and peritoneal biopsy	3 (3.3%)
Positive ovarian biopsy	3 (3.3%)
Tumor pathology (after chemotherapy), No. (%)	
Papillary serous histology	73 (81.1%)
Krukenberg	1 (1.1%)
Endometrioid	2 (2.2%)
MMMT	1 (1.1%)
Tumor grade, No. (%)	
High grade	69 (76.7%)
Moderate grade	3 (3.3%)
Low grade	1 (1.1%)
Recurrence, No. (%)	64 (71.1%)
Recurrence time (mon), Mean± SD	12.97±8.83
Survival, No. (%)	26 (28.9%)
Survival time (mon), Mean± SD	41.64±23.18

NACT, neoadjuvant chemotherapy; MMMT, malignant mixed Müllerian tumor.

After receiving NACT and performing surgery, papillary serous histology was reported in 73 (81.1%) of the women and other pathology reports were Krukenberg (1.1%), endometrioid (2.2%), and malignant mixed Müllerian tumor (MMMT) histology (1.1%). Pupillary serous histology in most participants was a high-grade type (76.7%), and only in 4 participants were low to moderate grade (4.3%). Moreover, 64 women (71.1%) had a recurrence of the disease at a mean time of 12.97 ± 8.83 months (Table 1).

The median pre-treatment CA-125 level was 980 U/mL (range 93-18550 U/mL), whereas the post-treatment CA-125 level was significantly reduced to median of 25 U/mL (range 2-1842 U/mL) (P<0.0001). There was

no significant difference in pretreatment CA-125 levels among the cytological subtypes ($P=0.815$).

In pupillary serosa pathology as the main pathology in the studied population, there was a significant difference between CA-125 before and after chemotherapy ($P<0.001$). In other pathologies (including endometrioid, pupillary serosa, and MMMT), CA-125 level had been reduced after chemotherapy (Table 2).

CA-125 levels after NACT had a significant positive correlation with age. The rate of CA-125 reduction after chemotherapy was also lower in older ages (r=0.274; $P=0.017$).

Relationship between survival and recurrence time with various variables are presented in Table 3. Survival time showed a significant and strong negative correlation with the CA-125 levels before (r=-0.363, $P=0.003$) and after chemotherapy (r=-0.383, $P=0.002$) Moreover, there was a significant negative correlation between survival time and chemotherapy courses (r=-0.363, $P=0.003$). Moreover, as shown in Table 3 recurrence time from surgery showed a significant and strong negative correlation with the CA-125 levels before (r=-0.404, $P=0.001$) and after chemotherapy (r=-0.238, $P=0.041$), Which means the recurrence time in patients with lower CA-125 was longer than the patients with higher CA-125.

Discussion

Based on the present study results, it can be said that the outcome of treatment can be affected by age, in other words the older ages negatively correlated with recurrence and survival times. Moreover, the rate of CA-125 reduction after chemotherapy was lower in older ages.

In previous studies, the patients assigned to receive NACT were usually older than their controls (16). It is generally believed that 15% to 20% of the patients with advanced ovarian cancer have pretreatment serum CA-125 level more than 35 U/mL (17-19). Moreover, in Markman et al study, in 6.9% of women with advanced ovarian cancer, CA-125 levels have remained normal (17). In this study, none of the participants had a pre-treatment serum CA-125 level 35 U/mL or lower. Furthermore, the findings of the present study showed the significant higher post chemotherapy CA-125 levels in the women who died or had lower survival time. Furthermore, lower levels of CA-125 could be a predictor of disease remission. previous studies showed that serum CA-125 levels depended on the survival rate of the patients with advanced ovarian cancer (20, 21). The results of a study by Kang and colleagues showed that there is a relationship between baseline serum CA-125 levels and survival rates after initial NACT. Patients with high serum CA-125 levels had lower survival rates than those whose serum CA-125 levels were normal after receiving chemotherapy (22). As previously mentioned, our results showed, survival time had a significant and strong negative correlation with the CA-125 levels before and after chemotherapy. A study showed the normalization of CA-125 levels (less than 35 U/ml) after receiving NACT was not a separate predictor of survival without progression or overall survival, but CA-125 after chemotherapy was a predictor independent of overall survival (23).

A study by Chan and co-workers showed that changes

Table 2. CA-125 Level Change Based on Pathology

Pathology After Chemotherapy	CA-125 Level (U/mL) (Before NACT)	CA-125 Level (U/mL) (After NACT)	*P* Value
Papillary serosa (n= 74)	990 (93-18550)	24 (2-1842)	<0.001*
Krukenberg (n= 1)	6338	-	-
Endometroid (n= 2)			-
Case 1	1550	8	
Case 2	141	118	
MMMT (n=1)	345	40	-

CA-125, Cancer antigen 125; NACT, neoadjuvant chemotherapy; MMMT, malignant mixed Müllerian tumor.
Data presented as median (range). [a]Wilcoxon test.

Table 3. Relationship Between Survival and Recurrence Time Various Variables

	Recurrence Time		Survival Time	
Variables	Correlation	Sig (2-tailed)	Correlation	Sig (2-tailed)
Age (y)	-0.227	0.061	-.0474**	<0.0001
Gravid	0.029	0.811	-.0218	0.77
Parity	0.015	0.905	-0.216	0.079
Abortion	0.146	0.230	-0.004	0.976
Chemotherapy courses	0.097	0.427	-0.363**	0.003
CA-125- before NACT	-0.404**	0.001	-0.363**	0.003
CA-125- after NACT	-0.238*	0.041	-0.383**	0.002

CA-125, Cancer antigen 125; NACT, neoadjuvant chemotherapy.
* Spearman correlation coefficient is significant at the 0.05 level.
** Spearman correlation coefficient is significant at the 0.01 level.

in CA-125 levels in advanced ovarian cancer could be predicted using the histology of EOC, but most the patients with high CA125 levels before receiving NACT had positive ascites cytology report (68.9%). Pupillary serous was the most frequent histology (81.1% of the included patients) (24). This histology type can be more critical because of the relationship between CA-125 level and survival rate due to a better prognosis of serous histology and endometrial histological groups (24). The results of our study showed that due to the decrease in serum CA-125 levels in the patients with advanced ovarian cancer treated with NACT, the clinical outcome, and survival of patients can be predicted.

Limitations of the Study

Finally, the most important limitation of the study was the small number of participations and no long-term follow-up.

Conclusions

Overall, the present study's findings showed an inverse association between serum CA125- levels and survival of patients receiving primary NACT in advanced ovarian cancer. In addition, our results showed that histological differences explain CA-125 changes in advanced ovarian cancer, and the treatment outcomes could be affected by age. The decrease in serum CA125 levels after chemotherapy was lower in older participants. The findings suggest that decreased serum CA125 levels in patients with advanced NACT-receiving ovarian cancer can predict clinical outcomes and patient survival.

Authors' Contribution

SA, YJ, and SSH designed the study and conducted the research. YJ, AM, and Mitra Modarres-Gilani monitored, evaluated, and analyzed the result of the study. Further, SA, YJ, and SSH reviewed the article. All authors approved the final manuscript and take responsibility for the integrity of the data.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

The research proposal was approved by the ethics committee of Tehran University of Medical Sciences, Tehran, Iran (Code: IR.TUMS.VCR.REC.1398.891) and the researchers were allowed access to the participants' medical records. Also, the ethical principles of the Helsinki Declaration and patient confidentiality were considered in all stages of this research.

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