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Original Research Article

Predictive value of changes in the serum CA-125 levels in patients undergoing interval debulking surgery after neoadjuvant chemotherapy in advanced epithelial ovarian carcinoma

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ABSTRACT

Background: The objective of this study is to evaluate the predictive value of serum CA-125 changes in the management of patients undergoing neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) in advanced epithelial ovarian carcinoma (EOC).
Methods: A retrospective hospital-based study of patients with advanced epithelial ovarian cancers (stage III and IV) was conducted at Department of Obstetrics and Gynecology in Gujarat Cancer and Research Institute, Ahmedabad, for two years. Total 50 patients were treated with NACT followed by surgical cytoreduction and followed up till August 2010. Response to NACT, optimal cytoreduction rate and overall response rate were analyzed.CA 125 levels before (baseline) and after NACT were analyzed.
Results: Out of 50, there were 43 patients (86%) with stage III disease and 7 (14%) with stage IV disease. Maximum 37(74%) patients had CA 125 levels >500 on presentation while none of the patients had baseline CA125 levels in the normal range (<35). Range of baseline CA 125 was 164-5394.All patients were given NACT and after NACT, out of 50 patients, 22(44%) patients had CA 125 values within the normal range (<35) while 23(46%) had values between 35 and 100. Thus, statistically significant difference (Z = 6.154, P<0.0001) was found between CA 125 level before and after NACT. Out of 45 patients with CA 125 <100, 35(77.8%) underwent optimal cytoreduction.
Conclusions: Baseline (prechemotherapy) serum CA-125 levels are powerful indicators of the presence and extent of spread of disease while CA-125 level particularly <100U/ml after NACT strongly predicts optimal cytoreduction in advanced epithelial ovarian cancers.

Keywords: Advanced epithelial ovarian cancer, Neoadjuvant chemotherapy, Serum CA-125 levels, Surgical cytoreduction

INTRODUCTION

Internationally, ovarian cancer (OC) is the seventh most commonly diagnosed cancer among women and 8th leading cause of cancer mortality among women.[1] Ovarian cancer has the lowest survival rate of all gynaecological cancers and is responsible for 140,000 deaths each year. A woman's lifetime risk of developing OC is 1 in 75, and her chance of dying of the disease is 1 in 100.[2] The disease typically presents at late stage when the 5-year relative survival rate is only 29%. In India, ovarian cancer is the third leading site of cancer among women, trailing behind cervical and breast cancer. Malignant OC, also known as carcinomas, are comprised of five main histotypes: high-grade serous (HGSOC; 70%), endometrioid (ENOC; 10%), clear cell (CCOC; 10%), mucinous (MOC; 3%), and low-grade serous (<5%).[3,4] Epithelial ovarian cancer has the highest case fatality ratio because more than two-thirds of patients have advanced disease at diagnosis (stage III and IV

classified by International federation of Gynecology and obstetrics).[5] According to American Cancer Society, invasive epithelial ovarian cancer is a disease associated with poor prognosis, with the 5-year survival ranging from 19 to 28%.

The need for the development of reliable serum biomarkers for early detection and prognostication of ovarian cancer, which are both sensitive and specific, remains a long-awaited priority. In the management of ovarian cancer these biomarkers have been applied for monitoring response to treatment, for distinguishing malignant from benign pelvic masses, for estimating prognosis, for predicting response to individual drugs, and for detecting primary disease at an early stage. Several epitopes on the polymorphic epithelial mucin derived from the MUC1 gene have been identified as targets for a family of tumor markers which include CA549, CASA (cancer associated serum antigen), CA19-9, CA15-3, MCA, MOV-1 and TAG72. The cytokeratin proliferation markers TPS and CYFRA21-1 have also been explored in ovarian carcinoma. Amongst these markers the most extensively researched is CA125.

The most widely used tumor marker in ovarian cancer, often considered the 'gold standard' is CA125.[6] It was first identified by Bast, Knapp, and colleagues in 1981. CA125 is a high molecular weight glycoprotein which is raised in approximately 90% of patients with advanced epithelial ovarian cancer.CA125 is expressed by fetal amniotic and coelomic epithelium and in adult tissues derived from the coelomic (mesothelial cells of the pleura, pericardium, and peritoneum) and Mullerian (tubal, endometrial, and endocervical) epithelia. CA125 contains 2 major antigenic domains, namely, A and B, which bind the monoclonal antibodies OC125 and M11, respectively. Since its development, measurement of the serum level of the CA125 antigen has become a standard component of routine management of women with advanced ovarian cancer. CA125 levels of less than 35 U/mL are now accepted as normal.[6] When stratified by disease stage, elevated levels were found in more than 90% of patients with advanced stage ovarian cancer but in only 50% of patients with stage I disease. In addition, elevated levels of CA125 are more strongly associated with serous, rather than mucinous tumors.[6]

Numerous studies have confirmed the usefulness of CA125 levels in monitoring the progress of patients with epithelial ovarian cancer.[7-10] Despite the well-characterized limitations in the interpretation of a solitary CA125 value, this biomarker is widely used to prospectively evaluate therapeutic efficacy and monitor disease status among ovarian cancer patients CA125 antigen is a serum marker which has been sufficiently well validated to be of use in routine clinical care . Thus, it is reasonable to seek to determine whether CA125 may have utility as a prognostic indicator and could in the future be used to individualize treatment of patients with ovarian cancer. The goal of this study is to evaluate the predictive power of serum CA-125 changes in the presence and extent of spread of disease and optimal cytoreduction in advanced epithelial ovarian cancers.

METHODS

A retrospective hospital-based study of advanced ovarian cancer (stage III and IV) was conducted at Department of Obstetrics and Gynecology.

Inclusion criteria

- Total 50 patients of advanced epithelial ovarian cancer stage III and IV were included for a period of 2 years.
- All patients with large volume ascites (>500 ml), extensive peritoneal disease and CA125 levels >500U/ml, not amenable for optimal cytoreduction patients and considered unresectable by the treating surgical team were subjected to NACT followed by surgical cytoreduction after obtaining an informed consent.

Exclusion criteria

- Patients who had significant primary surgical cytoreduction (any cytoreductive procedure other than exploratory laparotomy and biopsy) elsewhere were excluded from the study.

On presentation each patient was evaluated thoroughly by a detailed history regarding symptoms, past and family history. A thorough physical examination including Breast, neck, per abdomen, per speculum, per vaginal, per rectal examinations to assess ovarian mass, ascites, hepatosplenomegaly, peritoneal disease, pleural effusion, supraclavicular lymph nodes, was performed. Radiological examination either USG pelvis or CT scan and Chest X-ray to evaluate the extent of disease involvement and to decide staging and unrespectability. Serum CA 125 level was measured in every patient on presentation and graded whether <500 or >500 to assess the response to NACT and for prognosis. Histopathological confirmation (USG guided biopsy from the ovarian mass) was done in each case before starting NACT.NACT was started after establishing histopathological diagnosis. The commonest combination used was cisplatin and cyclophosphamide or paclitaxel and carboplatin every 21 days. Each patient was monitored for chemotherapy related adverse reaction graded according to WHO criteria. Response evaluation was done after 3rd/4th cycle of NACT and if there was no disease progression or tumor was responding, and if the disease was found clinically and radiologically respectable, patients were taken for interval cytoreductive surgery.

Serum CA 125 level was measured in every patient after NACT and graded <35, 35-100, 100-500, and >500 to assess the response to NACT and for prediction of

interval debulking surgery. Standard debulking procedure includes total abdominal hysterectomy, bilateral salpingo oopherectomy, total omentectomy, bilateral lymph node dissection and removal of other metastatic deposits. Response of NACT was assessed by extent of surgical resection possible (whether optimal or suboptimal debulking done). Patients were categorized as: Optimal debulking surgery-residual tumor <0.5cm in maximum diameter.[7] Suboptimal debulking surgery-residual tumor greater than or equal to 2cm in maximum diameter.[8] Data was collected and compiled in the excel sheet and analyzed with the appropriate statistical tests.

RESULTS

Total 50 patients were included in our study with advanced stage ovarian carcinoma who presented to our institute. Out of the total 50 patients, majority 43(86%) patients had stage III disease while only 7(14%) were stage IV disease with 5 patients having positive pleural fluid cytology and 2 patients with liver metastasis. 37(74%) patients had CA 125 levels>500 on presentation followed by 13(26%) with CA 125 levels 101–500 while none of the patients had baseline CA125 levels in the normal range (< 35). Range of baseline CA 125 was 164 - 5394. As depicted in Figure 1.

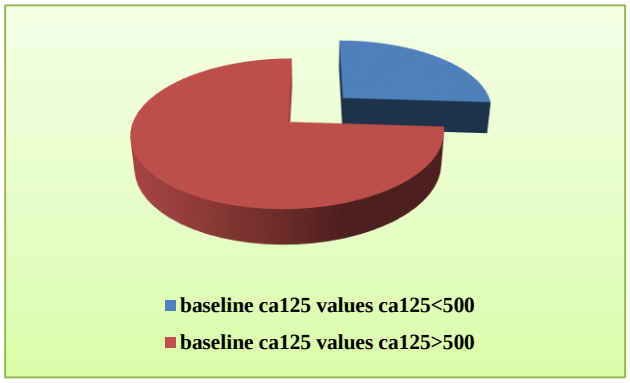

Figure 1: Distribution of baseline CA-125 values.

Out of 37 patients having CA-125>500,31(83.8%) patients had disease in pelvis well as per abdomen on USG while 3 patients had only pelvic disease. 3 patients had disease in abdomen that is ascites/liver/peritoneal metastasis with no evidence of pelvic mass on USG showing that CA125 >500 is indicative of advanced stage EOC in 74% of the cases. Table 1 shows relationship between baseline CA-125 levels and disease characteristics on USG before NACT.

Majority 36(72%) of the patients underwent optimal cytoreduction with residual disease <0.5cm while only 14(28%) patients had suboptimal cytoreduction with residual disease >2cm. Mean number of neoadjuvant CT cycles given were 3. After NACT 17(34%) patients had no evidence of disease on USG while 27(54%) had disease confined to pelvis only and 6(12%) had stable disease.

Table 1: Comparison of basal USG findings with baseline serum CA-125 levels.

Basal USG characteristics	Baseline serum CA-125 levels	Baseline serum CA-125 levels	Total
	>500 (%)	<500 (%)	
Disease in abdomen	3 (100)	0 (0.0)	3 (6)
Disease in pelvis	3 (18.8)	13 (81.3)	16 (32)
Disease in pelvis and abdomen	31(100)	0 (0.0)	31 (62)
Total	37 (74)	13 (26)	50 (100)

After NACT out of 50 patients, 22(44%) patients had CA-125 values within the normal range (<35) while 23(46%) had values between 35 and 100, 4(8%) had values between 100 and 500 with only one patient (2%) had CA 125 value >500 as compared to baseline(prechemotherapy)CA-125values where 37(74%) had >500. Thus, statistically significant difference (Z= 6.154, P<0.0001) was found between CA125 levels before and after NACT. As depicted in Figure 2.

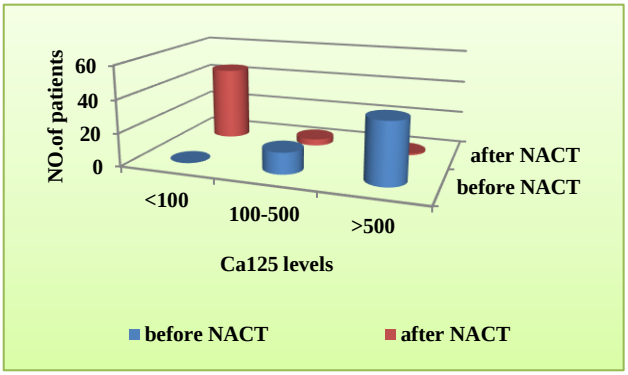

Figure 2: Changes in CA-125 levels before and after NACT.

Table 2 showed that out of 45 patients with CA125 <100, 35(77.7%) underwent optimal cytoreduction while only 1(20%) patient out of 5 having CA-125 >100 underwent optimal cytoreduction. Thus,97.2% of the patients who underwent optimal cytoreduction had CA-125 values <100 after NACT depicting statistically significant relationship between CA-125 values after NACT and optimal and suboptimal cytoreduction with a P value of 0.006 (<0.05).

After surgery, 31(62%) patients had CR at the end of treatment and were evaluable with a median follow up of 19 months. 3 patients (6%) had gross residual disease at the end of treatment called the primary refractory disease. 1 patient died due to disease. 5 patients were lost to follow up.2 patients (1+1LFU) had recurrence with a median PFS of 3.5 months.

Table 2: After NACT CA 125 levels and Interval debulking surgery (IDS).

IDS	CA-125 (%)		Total
	<100	**>100**	
Optimal	35 (97.2)	1 (2.8)	36 (72)
Sub optimal	10	4	14 (28)
Total	45	5	50 (100)

DISCUSSION

Numerous studies conducted since 1975 have reported that optimal cytoreduction, as opposed to suboptimal cytoreduction, improves the prognosis for patients with advanced EOC; however, the appropriate cutoff level separating the two has remained controversial. Currently, the Gynecologic Oncology Group defines optimal cytoreduction as a post-operative surgical residuum of ≤ 1 cm in largest diameter.[14] Recently, attention has focused on the incremental benefits of residual disease under 1 cm, specifically, no macroscopic residual disease (R0 resection). Chang et al reviewed 18 studies with a total of 13,257 patients and found that each 10% increase in the proportion of patients undergoing R0 cytoreduction was associated with a significant and independent 2.3-month increase (95% confidence interval [CI] = 0.6-4.0, p=0.011) in cohort median survival; each 10% increase in the proportion of patients undergoing cytoreduction to ≤1 cm residual disease was associated with a 1.8-month increase (95%CI=0.6-3.0,p=0.004) in cohort median survival.[15] These data suggest that patients with advanced stage ovarian cancer could only benefit from an optimal surgical debulking, which can lead to improved survival. Therefore, preoperative identification of patients most likely to have R0 resection is of paramount importance.

CA-125 levels can be a powerful predictor of optimal surgical cytoreduction. Many epidemiological studies have been carried out to this effect. Chi et al reported that preoperative serum CA-125 levels greater than 500 U/mL predicted suboptimal cytoreduction.[16] In 100 consecutive patients with stage III ovarian carcinoma, optimal cytoreduction (residual tumor ≤1cm) was achieved in 33 of 45 patients (73%) with a CA-125 level <500U/mL, compared to only 12 of 55 patients (22%) with a CA-125 level>500 U/mL (P<0.001).

In present study 86% of patients were in stage III, like Le et al.[7] Majority (74%) of the patients had baseline CA125 values >500U/ml showing that baseline CA125 >500 is indicative of advanced stage EOC.

After NACT normalization of CA125 value (<35U/ml) was found in 22(44%) patients while 90% patients had value <100U/ml. Thus statistically significant (P<0.0001) reduction in CA125 was found similar to findings of Le T et al, and Le T, Williams et al.[7,8] Out of 22(44%) patients having CA125 <35 that is within normal range, 17(77.3%) underwent optimal cytoreduction hence a pre-IDS CA-125 level less than 35 U/mL is an independent predictor of complete IDS similar to findings of Furukawa N et al[12].These results show that changes in serum CA-125,particularly CA125 value <100U/ml can predict optimal cytoreduction to no gross residual disease in patients with advanced stage ovarian cancer treated with neoadjuvant chemotherapy similar to findings of Rodriguez N et AL, while in the study conducted by Zeng J, Yin J et al, a preoperative CA125 of ≤200 U/ml was an independent predictor of optimal cytoreduction to no visible residual disease in patients treated with NACT.[9,13]

The retrospective nature of the study design can be our limitation; hence the results of our current study should be confirmed in a large, well-designed prospective study.

CONCLUSION

The results of the study show that Baseline (prechemotherapy) serum CA-125 levels particularly >500U/ml are powerful indicators of the presence and extent of spread of disease in advanced epithelial ovarian cancer while CA-125 level particularly <100u/ml after NACT strongly predicts optimal surgical cytoreduction, which in turn leads to improved survival in advanced epithelial ovarian cancers.

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