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Changes in serum CA-125 can predict optimal cytoreduction to no gross residual disease in patients with advanced stage ovarian cancer treated with neoadjuvant chemotherapy

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ABSTRACT

Objective. To evaluate the predictive power of serum CA-125 changes in the management of patients undergoing neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS) for a new diagnosis of epithelial ovarian carcinoma (EOC).

Methods. Using the Cancer Registry databases from our institutions, a retrospective review of patients with FIGO stage IIIC and IV EOC who were treated with platinum-based NACT-IDS between January 2006 and December 2009 was conducted. Demographic data, CA-125 levels, radiographic data, chemotherapy, and surgical–pathologic information were obtained. Continuous variables were evaluated by Student's *t* test or Wilcoxon–Mann–Whitney test.

Results. One hundred-three patients with stage IIIC or IV EOC met study criteria. Median number of neoadjuvant cycles was 3. Ninety-nine patients (96.1%) were optimally cytoreduced. Forty-seven patients (47.5%) had resection to no residual disease (NRD). The median CA-125 at diagnosis and before interval debulking was 1749 U/mL and 161 U/mL, respectively. Comparing patients with NRD v. optimal macroscopic disease (OMD), there was no statistical difference in the mean CA-125 at diagnosis (1566 U/mL v. 2077 U/mL, $p = 0.1$). There was a significant difference in the mean CA-125 prior to interval debulking, 92 v. 233 U/mL ($p = 0.001$). In the NRD group, 38 patients (80%) had preoperative CA-125 $\leq$ 100 U/mL compared to 33 patients (63.4%) in the OMD group ($p = 0.04$).

Conclusions. Patients who undergo NACT-IDS achieve a high rate of optimal cytoreduction. In our series, after treatment with taxane and platinum-based chemotherapy, patients with a preoperative CA-125 of $\leq$100 U/mL were highly likely to be cytoreduced to no residual disease.

Introduction

Epithelial ovarian carcinoma (EOC) is the leading cause of death due to a gynecologic malignancy in the United States. In 2010, there were approximately 21,880 new ovarian cancer cases and 13,850 deaths with over 70% of women with newly diagnosed EOC presenting with advanced stage disease [1]. Primary debulking surgery (PDS) followed by platinum based chemotherapy has been considered the standard of care for advanced ovarian cancer [2–10]. However, the results of a recent randomized controlled trial which compared PDS to neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS) in patients with advanced EOC demonstrated similar progression free survival and overall survival among the two groups [11]. Among both groups, complete resection of all macroscopic disease was the strongest independent variable in predicting overall survival. Therefore, it is important to identify a reliable clinical strategy that can predict the likelihood of achieving resection to no residual disease.

Previous studies have attempted to use preoperative computed tomography (CT) [12,13] and preoperative CA-125 levels [14,15] to predict optimal PDS in patients with advanced stage ovarian cancer. However, the radiologic studies were limited by their low sensitivity, low positive predictive value, and lack of reproducibility. Preoperative CA-125 levels to predict optimal PDS yielded mixed results. The goals of the current study were to evaluate the changes in serum

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CA-125 and patient characteristics to predict the likelihood of achieving optimal interval cytoreduction in patients undergoing taxane and platinum-based neoadjuvant chemotherapy followed by interval debulking surgery for a new diagnosis of advanced stage ovarian cancer and to determine an ideal number of neoadjuvant chemotherapy cycles before attempting interval debulking surgery. A secondary aim of our study was to identify factors associated with platinum resistance in patients receiving neoadjuvant chemotherapy.

Patients and methods

Institutional Review Board approval of the study was obtained from both participating institutions. All patients with advanced stage EOC who were treated with NACT-IDS between January 1, 2006 and December 31, 2009 were identified from the cancer registry databases at the Brigham and Women's Hospital (BWH) and the Massachusetts General Hospital (MGH). Some patients were diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage IIIC or IV EOC by formal staging criteria, some were noted to have advanced disease radiographically and determined to be unresectable by the primary surgeon, and others had a performance status that precluded PDS. Demographic data, chemotherapy regimen and number of cycles, surgical-pathologic information, CA-125 levels at diagnosis, before each treatment cycle, and prior to interval debulking surgery were retrospectively obtained from patient medical records, as was timing of recurrence and/or disease status at last follow-up. The decision to perform PDS vs. NACT-IDS was based on the attending physician's judgment. In addition, chemotherapy regimen and the number of cycles that the patient received were determined by the patient's treating oncologist. Debulking surgery was performed by board eligible/board certified gynecologic oncologists. All patients underwent an exploratory laparotomy with the intention of achieving optimal cytoreduction. An operation that left the patient with a maximal diameter of ≤1 cm residual disease was considered optimal. All operative and pathologic reports were reviewed by two individuals.

Following initial eligibility screening, the following inclusion criteria were applied to determine the final study population: (1) an elevated serum CA-125 at time of diagnosis (>35 U/mL); (2) at least two serum CA-125 level determinations (at the time of diagnosis and prior to IDS); and (3) clinical and/or radiographic determination of disease status at the time of last follow-up or recurrence. Definitive diagnosis of recurrence was taken as a rising CA-125, the histologic presence of cancer at the time of secondary cytoreductive surgery and/or the appearance of new lesions by CT scan or by positron emission tomography (PET) scan imaging. Patients were excluded from the study for the following reasons: surgery performed at another institution, incomplete surgical–pathologic data, and non-platinum and taxane based neoadjuvant chemotherapy.

Platinum-sensitive disease was defined as patients who relapsed more than 6 months after completing platinum therapy. Platinum-resistant was defined as patients that have relapsed within 6 months of prior platinum therapy. Finally, platinum-refractory disease was defined as disease that progressed or was stable during initial platinum therapy.

For statistical analyses, standard univariate logistic regression models were used to compare absolute and percent changes (predictor variables) in serum CA-125 levels among patients with no visible residual disease (NRD) and optimal cytoreduction but macroscopic disease ≤1 cm (OMD)(outcome variables). Absolute changes were calculated by subtracting the CA-125 at diagnosis from the CA-125 level within 30 days of surgery. Relative changes were calculated as a percentage of the CA-125 level within 30 days of surgery and the CA-125 at diagnosis.

Continuous variables were evaluated by Student's *t* test or Wilcoxon–Mann–Whitney test, as appropriate. Categorical variables were evaluated by chi square test or Fisher's exact test as appropriate for category size. Standard univariate analyses were performed, as were multivariable analysis with logistic regression to control for potential confounding variables. For continuous variables, the cutoff level chosen was their median value, unless otherwise specified. All statistical tests were 2-sided and differences were considered statistically significant at $P<0.05$. Data analysis was performed with SPSS statistical software (version 18.0, SPSS, Inc, Chicago, IL).

Results

A total of 113 patients who received NACT during the study period were identified. Ten patients were excluded for the following reasons: nine patients did not have CA-125 level determinations at the time of diagnosis or within 30 days of interval debulking surgery. One patient received only platinum based chemotherapy and was excluded. The final analysis included 103 patients with advanced stage ovarian cancer who received platinum and taxane-based NACT and all of whom underwent cytoreductive surgery. The median age of the study population was 66 years (range, 44–85 yo). Forty-one

Table 1
Patient characteristics.

	NRD (N=47)		OMD (N=52)		p-Value
Age (years)	66	(±9)	66	(±10)	0.5
Stage					
IIIC	18	28.30%	21	40.40%	0.2
IV	29	61.70%	31	59.60%	
Time to surgery (days)	102	(±48)	102	(±45)	0.3
Chemotherapy					
Platinum	47	100%	52	100%	0.9
Taxol	47	100%	52	100%	
Cycles of neoadjuvant chemotherapy					
≤3	25	53.10%	25	48%	0.8
>3	22	46.90%	27	52%	
CA-125 U/mL presentation	1566	(±1810)	2077	(±2900)	0.1
CA-125 U/mL preoperatively	92	(±139)	233	(±492)	0.001
CA-125≤100 U/mL preoperatively	38	80.00%	33	63.40%	0.04
Change CA-125 presentation to preop (%)	86	(±18)	86	(±16)	0.07
Change CA-125>80% presentation to preop (%)	36	76.50%	38	73%	0.06
Hysterectomy	47	100%	52	100%	0.9
Bilateral salpingo-ophorectomy	47	100%	52	100%	0.9
Omentectomy	47	100%	52	100%	0.9
Bowel surgery	12	25.50%	19	36.50%	0.3
Splenectomy	7	14.20%	5	9.60%	0.6
Diaphragmatic surgery	3	6.30%	11	21.10%	0.1
Liver surgery	0		3	5.70%	0.3