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CA125 kinetic parameters predict optimal cytoreduction in patients with advanced epithelial ovarian cancer treated with neoadjuvant chemotherapy

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HIGHLIGHTS

- This paper aims at determining the optimal CA125 cut-off value to accurately predict complete cytoreduction after NAC.
- A CA125 level <75 UI/ml after the 3rd NAC was an independent predictor factor for complete surgery.

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ABSTRACT

Objective. To evaluate the different kinetic parameters of serum CA125 during neoadjuvant chemotherapy (NAC) to predict optimal interval debulking surgery (IDS).

Methods. The present retrospective multicenter study included patients with advanced ovarian cancer treated with neoadjuvant platinum-based chemotherapy followed by IDS between 2002 and 2009. Demographic data, CA125 levels, radiographic data, chemotherapy and surgical-pathologic information were obtained. Univariate and multivariate analyses were performed to evaluate variables associated with complete IDS. ROC analysis was used to determine potential cut-off values to predict the likelihood of complete cytoreduction via IDS.

Results. One hundred and forty-eight patients met the study criteria. Ninety-three patients (62.8%) had optimal cytoreduction with no residual macroscopic disease (CC-0) after IDS. In multivariate analyses, the CA125 level after the 3rd NAC was an independent predictor for optimal cytoreduction (odds ratio: 0.98 [0.97–0.99], $p = 0.04$). The area under the ROC curve was 0.73. A threshold of 75 UI/ml displayed the most predictive power. The odds ratio to predict complete cytoreduction was 3.29 [1.56–7.10] ($p = 0.0008$).

Conclusion. Our data indicate that for advanced ovarian cancer, a CA125 level less than 75 UI/ml after the 3rd NAC was an independent predictor factor for complete IDS.

Introduction

Epithelial ovarian carcinoma is the leading cause of death among gynecological malignancies in Europe. At the time of diagnosis, approximately 75% of women with ovarian cancer have advanced stage disease [1]. Many authors reported rates of optimal interval debulking surgery (IDS) after neoadjuvant therapy (NAC) ranging from 41.5% to 94% [2–4]. Various parameters have been proposed to evaluate the ability to initial complete resection, and several studies reported a correlation between CA125 levels and resectability in primary debulking setting. Pre-IDS evaluation must necessarily be subject to the same requirements for rigor. In addition to imaging devices, CA125 levels may help to predict complete resection after NAC. Only two studies have investigated the kinetic parameters of CA125 as a predictor of optimal interval debulking surgery. One report concluded that patients with preoperative CA125 level of less than 100 UI/ml were highly likely to be cytoreduced with no residual disease [5]. Additional data are needed to define the optimal threshold of CA125.

The aim of the current study was to evaluate the kinetic parameters of serum CA125 in patients with advanced epithelial ovarian cancer who were treated with neoadjuvant chemotherapy to determine the optimal CA125 cut-off value to accurately predict complete cytoreduction after NAC.

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Materials and methods

Patient selection

After IRB approval (number 2013–10), we conducted a multicenter retrospective study, based on databases from the Curie Institute, René Huguenin Center and Tenon Hospital. Patients who received NAC based platinum for epithelial ovarian carcinoma, as verified histologically, between January 2002 and December 2009 were included in this study. Eligible patients had biopsy-proven deemed not optimal resectable epithelial ovarian carcinoma. The patients underwent laparotomy or laparoscopy exploration with minimal surgery, followed by NAC, interval debulking surgery and adjuvant chemotherapy. For each patient, the following clinical, biochemical, radiological and pathological variables were collected: age, weight, personal and family history, genetic predisposition, characteristics of disease (histology, stage, and surgery) and relapse (treatment-free interval, location, and management).

Measurement of CA125

For each patient, all available serum CA125 measurements were collected. CA125 concentrations were determined in the laboratories of three centers, and CA125 levels from pre-NAC to pre-IDS were recorded. CA125 levels were measured initially (5 days ± 2.6 before first course of chemotherapy) then the day of the following chemotherapy, interval between 2 courses/measures: 22 days ± 5.6. Before 2007, the Cisbio international "ELSA-CA125 II", a solid phase two-site immunoradiometric assay, was used. Since 2007, the B-R-A-H-M-S CA125 II Kryptor^R technique, an automatic immunofluorescence analysis kit to measure CA125 in the serum or plasma, was used to assay CA125.

A concentration of CA125 ≤ 35 UI/ml was considered normal.

Statistical analysis

The kinetic parameters of CA125 levels were studied in the following contexts: CA125 levels after each cycle of chemotherapy, nadir, time to normalization, percentage of decrease after NAC, and the slope of decline. To assimilate the decline in CA125 levels to a drug given as an intravenous bolus, we parameterized the apparent CA125 elimination in terms of apparent clearance. A four-parameter logistic curve fit function was used to model CA125 kinetics. Continuous variables were evaluated by Student's t test or Wilcoxon–Mann–Whitney test, as appropriate. For categorical variables, chi-square or Fisher's exact tests were used. Standard univariate analyses were performed to compare the absolute and percent changes in serum CA125 among patients with optimal tumor cytoreduction after interval debulking surgery. To assess prognosis and peritoneal surface malignancy, we used the completeness of cytoreduction (CC) score: CC-0 is defined as no residual macroscopic lesion after cytoreduction [6]; CC-1, 2 and 3 (CC-1+) score (tumor nodules persisting after cytoreduction less than 2.5 mm, between 2.5 mm and 2.5 cm, and greater than 2.5 cm or a confluence of unresected tumor nodules, respectively) were grouped together. Multivariate analyses were performed using a logistic regression model to control for potential confounding variables. Significant variables in univariate analysis were included in this model.

ROC analysis was used to determine the optimal threshold of CA125 levels to predict of the possibility of CC-0 after interval debulking surgery. The area under the ROC curve corresponds to the overall predictive validity. The 95% CI was calculated using a bootstrap method. A value of 1 corresponds to a perfect accuracy measure and a value of 0.5 indicates pure chance. A predictive model using logistic regression determined the optimal threshold using Presence Absence package. The odds ratios were calculated with a confidence interval of 95%. To calculate misclassification error rates we defined the best predictor using the Youden point on the ROC curve. The Youden index (YI) is defined as maximum (sensitivity (YP) + specificity (YP) − 1), occurring at the optimum threshold which is the Youden point (YP) [7]. Differences were considered statistically significant at $p < 0.05$. CC-1+ as the outcome occurred and a CA125 value >75 UI/ml after the 3rd NAC were used to calculate sensitivity, specificity, positive and negative predictive value. Overall survival (OS) and relapse-free survival (RFS) were estimated by the Kaplan–Meier method and compared using the log-rank test. The OS was the time from date of diagnosis until death from any cause. The RFS was defined as any disease recurrence (either measurable lesion or evidence of CA-125 greater than, or equal to, 2 times the upper limit of the reference range/nadir on 2 occasions at least 1 week apart) from the end of treatment. Data analyses were performed using R Version 3.2.2 software.

Results

The final analysis included 148 patients with advanced stage ovarian cancer who received platinum and taxane-based NAC followed by interval debulking surgery (IDS). The mean age of the study population was 62 years (range, 21 to 83 years). One hundred and seven patients (72.3%) had stage IIIc disease, and 35 (23.6%) patients had FIGO stage IV (International Federation of Gynecology and Obstetrics) disease. One hundred and thirteen (76.3%) patients had a papillary serous adenocarcinoma. Optimal interval cytoreduction with no residual disease (CC-0) was achieved in 93 patients (62.8%). The median CA125 levels at diagnosis and prior to IDS were 1079 UI/ml (range, 15 to 26,220 UI/ml) and 22 UI/ml (range, 1.7 to 3478), respectively. The mean number of neoadjuvant cycles was 5.6 (range, 1 to 9) with a median of 6 cycles. Because all of the patients in our study population had IDS, we compared patients with no residual disease (CC-0) vs patients with residual disease (CC-1+). Table 1 summarizes patient demographic and clinical characteristics. There was no significant difference in the median CA125 level at diagnosis in patients with CC-0 compared to patients with CC-1+ (1013 UI/ml vs. 1267 UI/ml, $p = 0.5$). However, the median CA125 level prior to IDS was lower for patients with CC-0 compared to patients with CC-1+ (19 UI/ml vs. 43 UI/ml, $p < 0.01$).

In the univariate logistic analysis, the CA125 level after the 3rd NAC and cycle to nadir were significantly associated with the possibility

Table 1
Demographic and clinical characteristics.

Characteristics	Overall population	CC-0 (n = 93)	CC-1+ (n = 55)	p-Value
Age (years)	62.3	62.2	62.5	0.86
BMI (kg/m^2)	23.8	23.5	24.3	0.20
Gestity	2.3	2.29	2.30	0.85
Parity	1.8	1.86	1.90	0.78
Menopause	89.1%	87.3%	90.3%	0.57
Family history of cancer	43.2%	41.9%	50%	0.66
Personal history of cancer	16.2%	17.2%	14.5%	0.67
Histology				
serous adenocarcinoma	76.3%	79.6%	71%	0.32
other	23.7%	20.4%	29%	
Grading				
I	5.5%	6.4	4.1%	0.54
II	42%	45.4	36.7%	0.33
III	52.4%	48%	59%	0.22
FIGO stage				
IIIc	72.3%	74.2%	69%	0.51
IV	23.6%	20.4%	29.1%	0.24
Pre-NAC CA-125 (UI/ml)	2122 [15–26,220]	1929 [15–11,750]	2467 [77–26,220]	0.33
Cycles of NAC	5.6	5.6	5.5	0.693
Relapse before 12 months	61.9%	46.2%	59.1%	<0.00001

CC-0, non residual disease after interval debulking surgery (IDS); CC-1+, residual disease after IDS; BMI, body mass index.