Dynamic Analysis of CA125 Decline During Neoadjuvant Chemotherapy in Patients with Epithelial Ovarian Cancer as a Predictor for Platinum Sensitivity

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Abstract. *Aim: Our objective was to evaluate the kinetic parameters of serum CA125 during neoadjuvant platinum-based chemotherapy (NAC), in patients with epithelial ovarian cancer, in order to identify a surrogate marker of sensitivity to platinum. Materials and Methods: Patients diagnosed between 2002 and 2009, and treated with NAC and interval debulking surgery, were included in the study. Results: One hundred and forty-two patients met the study inclusion criteria. Fifty-four patients (38%) were platinum-sensitive (PFI >12 months). A CA125 level after the 3rd NAC cycle <35 UI/ml was significantly associated with improved overall survival (OS) and relapse-free survival (RFS). In the multivariate model, patients with a CA125 level after the 3rd NAC cycle >35 UI/ml were 3.8-times more at risk for PFI <12 months (95% CI=1.7-8.5, p<0.001). Conclusion: A CA125 level after the 3rd NAC <35 UI/ml is an independent predictor for tumor platinum-sensitivity.*

Despite progress in the management of ovarian cancer during the last decade, diagnosis is delayed, with 70% of patients diagnosed at an advanced stage (FIGO stages III and IV) (1-2). The prognosis is poor; with a 5-year overall survival for all stages combined being only 20%. The standard upfront treatment consists of maximal cytoreductive surgery followed by adjuvant chemotherapy with platinum-taxane combination regimen. Although response rates are in the range of 70-80% (3), the majority of these patients will eventually relapse and are deemed incurable. Upon recurrence, the choice of second-line chemotherapy is guided by the duration of response to the prior platinum-based chemotherapy, that is, platinum-free interval (PFI). Several studies of platinum sensitivity have classified groups of patients according to the time to recurrence with the following categories: between 0 and 6 months (refractory or resistant), between 6 and 12 months (partially sensitive), beyond 12 months (platinum-sensitive). The prognosis is poor for patients who progress during treatment (platinum-refractory) or for those whose disease recurs within 6 months (platinum-resistant), with a median overall survival of 9 months. In contrast, platinum-sensitive cancers have much better prognoses with a median overall survival of 3 years and a response rate to platinum re-treatment between 50% and 70% (4, 5). Actually, controversies and uncertainties still exist in the partially platinum-sensitive population regarding the best treatment and the most effective therapeutic agents, because the response rate to subsequent platinum retreatment has been reported to be only 25-30%. Few recent studies have shown that non-platinum agents could be more effective than platinum-based therapy in this subset of patients. Moreover, it was shown that platinum would reverse resistance, or increase sensitivity to and response to subsequent platinum re-treatment (6-11). Neoadjuvant platinum-based chemotherapy is therefore often performed for patients with advanced ovarian cancer, followed by interval debulking surgery. Surgery is less aggressive, so less morbid, with a similar relapse-free (RFS) and overall survival (OS) compared to standard management (12-16).

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Serum cancer antigen 125 (CA125) is the representative tumor marker of ovarian cancer. The interest in CA125 level has already been studied extensively for standard management and monitoring of epithelial ovarian cancer. Few studies have been recently conducted regarding CA125 parameters during neoadjuvant chemotherapy (NAC) and the prognosis of advanced ovarian cancer. Different approaches have been used to analyze tumor marker decrease following anticancer treatment (regression coefficient (17), timing of normalization (18), nadir concentration (19)). The most appropriate method has not yet been determined. Moreover, conclusions remain unclear; this would mean non-use of these results in our clinical practice.

In this study, we evaluated the kinetic parameters of CA125 during neoadjuvant platinum-based chemotherapy in order to identify a surrogate marker of platinum sensitivity.

Materials and Methods

Patient selection. After IRB approval, we conducted a multicenter retrospective study, based on databases of the Curie Institute, René Huguenin Center and Tenon Hospital. Patients who received NAC-based platinum for epithelial ovarian carcinoma, histologically verified, between January 2002 and December 2009 were included in the study. 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. 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. Statistical analyses were performed with R Version 3.2.2 software. The Wilcoxon-Mann-Whitney test was used for the analysis of quantitative variables, and the Chi-square or Fisher's exact tests were used for qualitative variables. The overall survival and relapse-free rates were estimated using the Kaplan-Meier method and compared using the log-rank test. Logistic regression model and Cox regression analysis were used to determine independent factors (stepwise analysis selection of variables significantly associated with outcome in the univariate analysis). Odds ratio were calculated with a confidence interval of 95%. A $p<0.05$ was considered significant.

The following kinetic parameters of CA125 levels were studied: CA125 levels after each cycle of chemotherapy, nadir, timing of normalization, percentage of decrease after NAC, slope of decline. Assimilating the CA125 decline to a drug given with an intravenous bolus, we parameterized the apparent CA125 elimination in terms of apparent clearance. A four-parameter logistic curve fit function was used for modeling CA125 kinetic. The four parameter log-logistic model can be expressed as follows:

$$f(x,(b,c,d,e)) = c + \frac{d-c}{1 + exp\{b(log(x) - log(e))\}}$$

with 4 parameters b, c, d, e. The parameter e is the time at half-maximal effect between the upper limit, d, and lower limit, c. The parameter b denotes the relative slope around e (Figure 1). ROC analysis was used to determine the optimal threshold of CA125 levels to predict of platinum-sensitivity. The area under the ROC curve corresponds to the overall predictive validity. 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 the 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) (20).

The platinum-free interval (PFI) is defined as the interval from the end of platinum-based chemotherapy to first recurrence. We chose the threshold value of 12 months to qualify a platinum-sensitive disease. The diagnosis of recurrence based on clinical symptoms, clinically detectable disease and/or radiological evidence of disease recurrence. 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; 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.

Results

A total of 142 patients were eligible for analysis, and were grouped based on their PFI (relapse <12 months or >12 months of completion therapy). Only two patients demonstrated normal CA125 level at the time of diagnosis, one in each group. Median follow-up was 38 months (range=5.3-126 months). Fifty-four patients of 142 (38%) showed a platinum-sensitive disease (PFI >12 months). We also compared patients and tumor characteristics between patients with sensitive or non-sensitive disease. Patient characteristics for study groups are summarized in Table I. The median age of patients was 62.2 years (range=21-83 years). Eighty-nine percent of patients were in menopause. The diagnosis of ovarian cancer was established by: peritoneal biopsy in 43% of cases (n=61), adnexectomy in 36% of cases (n=51), ascites fluid 7% (n=10), ovarian biopsy 5% (n=7) and pleural aspiration less than 1% of cases (n=1). One hundred and thirty-two patients had a surgical exploration before neoadjuvant chemotherapy (93%). The exploration was performed by laparoscopy in 53% of cases. The average BMI was 23.7 kg/m^2. The majority of patients (90.5%) had serous adenocarcinoma and 83.7% had tumors that were grade 2 or 3 on final pathology, using the Shimizu/Silverberg system. When analyzing demographics and pathological characteristics, no significant differences were observed between platinum-sensitive and platinum resistant/intermediate

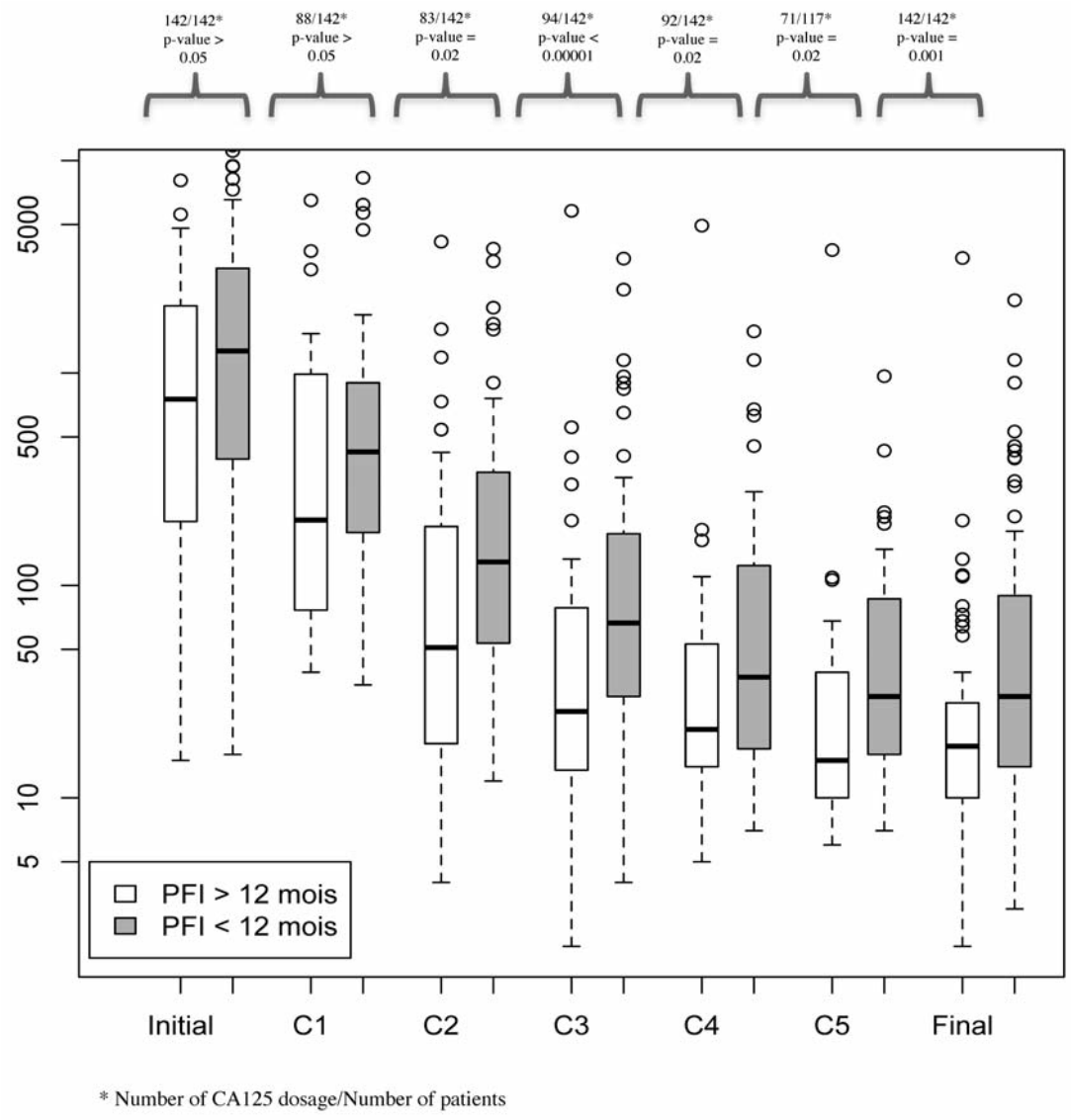

Figure 1. *Evolution of the CA125 level during neoadjuvant chemotherapy.*

patients (Table I). The majority of patients received 4 to 6 cycles of neoadjuvant platinum-based chemotherapy. The mean of pre-NAC CA125 level was 2,526 UI/ml (range=16-1,6275 UI/ml) in patients showing relapse before 12 months and 1,504 UI/ml (range=15-8,068 UI/ml) in those relapsing after 12 months group, without significant difference between groups. The mean percent decline in serum CA125 immediately after NAC was 90.5% in the PFI <12 months group and 93.3% in the PFI >12 months group; there was not a significant difference between the two groups. Using univariate logistic analysis, the factors significantly associated with relapse after 12 months were CA125 level after the 2nd and the 3rd NAC, final CA125 level, slope of half-life, half-life and nadir-cycle (Table II and Figure 2). In multivariate analysis, the only independent predictive factors of platinum-sensitivity were CA125 level after the 3rd NAC and nadir-cycle (Table II). The optimal threshold for CA125 level after the 3rd NAC to predict platinum-sensitivity was determined by ROC curve. The sensitivity and specificity of CA125 level after the 3rd NAC that is greater than 35 UI/ml were 73.8% and 64.8% respectively; with a positive predictive value of over 77% to predict relapse <12 months. The area under the curve was 0.75 (95%CI=0.67-0.82). In the multivariate analysis, the odds ratio for relation between CA125 after the 3rd ≥35 UI/ml and relapse <12 months was 3.8 with a 95% confidence interval of 1.7 to 8.5 (p<0.001).

Table I. *Patient and tumor characteristics*.

Characteristics	Overall population	PFI <12 months (n=88)	PFI >12 months (n=54)	*p*-Value
Age (mean±standard deviation)	62.2±10.4	63.2±10.7	61.4±9.8	0.217
BMI (kg/m^2)	23.7±3.7	24±3.7	23.7±3.7	0.842
Gestity (mean±standard deviation)	2.3±1.9	2±1.8	2.6±2	0.051
Parity (mean±standard deviation)	1.9±1.7	1.7±1.7	2±1.8	
Menopause	89.1%	89.9%	88.9%	0.856
HRT medication	32%	37.1%	27.1%	0.255
Family history of cancer	43.2%	40.5%	48.1%	0.384
Personal history of cancer	16.2%	15.2%	16.7%	0.819
Histology				
Adenocarcinoma	85.1%	86.3%	84.9%	0.828
Cystadenocarcinoma	13.5%	12.5%	15.1%	0.182
Serous	90.5%	92.5%	90.6%	0.692
Mucinous	1.3%	2.5%	0	0.359
Endometrioid	4.7%	3.8%	5.7%	0.4524
Clear cells	4%	3.8%	5.7%	0.4524
Grading				
I	4.7%	5.6%	6.7%	0.8206
II	35.8%	39.4%	42.2%	0.766
III	47.9%	54.9%	51.1%	0.689
FIGO stage				
IIIc	75.3%	70%	74.1%	0.609
IV	24.6%	26.3%	20.4%	0.435
Pre-NAC CA-125 (UI/ml) (mean, range)	2128.7 (15-16275)	2245.4 (16-16275)	1504.07 (15-8068)	0.1426
Cycles of NAC (mean, range)	5.6	5.6	5.5	0.693
Cytoreduction (interval surgery)				
CC0	62.7%	48.9%	83.3%	
CC1-2	37.3%	51.1%	14.8%	0.00005

PFI, Platinum-free interval; BMI, body mass index; HRT, hormone replacement therapy; FIGO, International Federation of Gynecology and Obstetrics; NAC, neoadjuvant chemotherapy.

Table II. *Univariate and multivariate analysis of serum CA125*.

Variables	PFI <12 months (n=88)	PFI >12 months (n=54)	Univariate *p*-value	Multivariate OR [95% CI]	Multivariate *p*-value
Initial level of CA125*	2526 UI/ml (16-16275)	1504 UI/ml (15-8068)	0.11		
CA125 after the 1st NAC cycle*	855 UI/ml (34-8300)	795 UI/ml (39-6500)	0.19		
CA125 after the 3rd NAC cycle*	336 UI/ml (4-3456)	186 UI/ml (1.7-5799)	0.00001	3.8 [1.7-8.5]	0.001
Normalization after the 3rd NAC cycle	23 (26%)	35 (65%)	0.00001		
CA125 after all courses of NAC*	120 UI/ml (3-2200)	94 UI/ml (1.7-3478)	0.001		
Half-life of CA125	42 days	33 days	0.01		
Slope at half-life	7.7 UI/d	6.5 UI/d	0.65		
Cycle to nadir*	4.9 (1-9)	3.8 (1-6)	<0.00001	2.0 [1.5-2.7]	<0.0001
Percent of decrease	93.3%	90.5%	0.28		

*Mean and range.

The estimated median overall survival for the current study cohort was 40.6 months, and the relapse-free survival was 8.9 months. The overall survival showed a significant difference between those with a normal CA125 level after the 3rd NAC cycle (<35 UI/ml) *vs.* ≥35 UI/, and the median overall survival was 50 months *versus* 36 months respectively ($p<0.0001$). Similar results were observed in relapse-free survival time, with 13.8 months *versus* 7.4 months, respectively (Figure 3). In a multivariate Cox regression, CA125 level after the 3rd NAC cycle <35 UI/ml ($p=0.02$), nadir-cycle ($p=0.001$) and complete cytoreduction ($p=0.02$) were associated with overall survival.

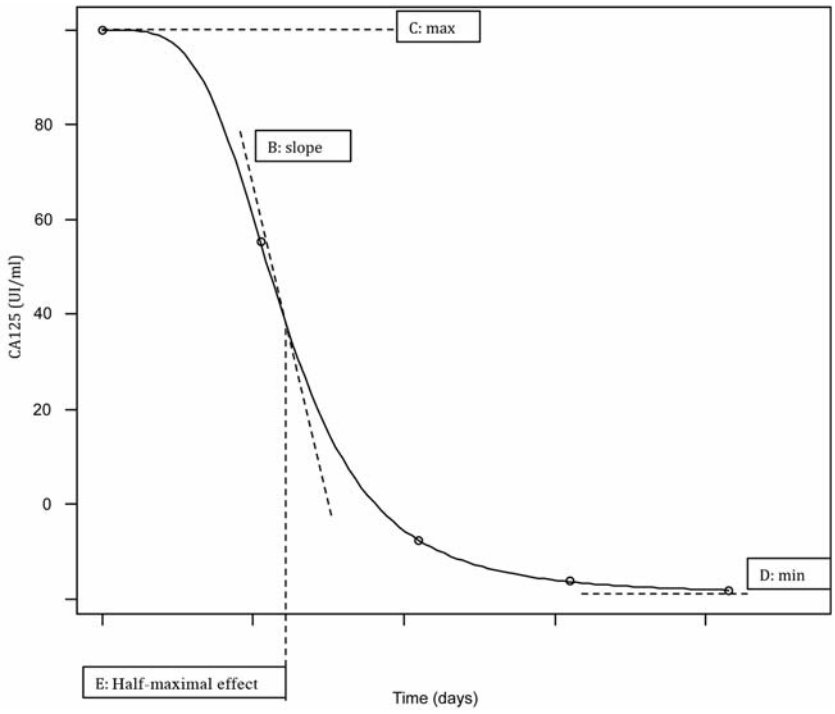

Figure 2. *Four-parameter logistic curve fit function was used for modeling CA125 kinetic (↓ course of chemotherapy).*

Discussion

The prognostic factors of advanced ovarian cancer include the amount of residual tumor after surgery, histological type and grade, performance status and age (21-22). Few studies have investigated cohorts of patients receiving NAC, and only occasional studies have examined the kinetic parameters of CA125 during treatment. The majority of these studies analyzed the association between CA125 and survival, using sometimes complex kinetic parameters. Riedinger *et al*. first introduced the concept of CA125 bi-exponential decrease, in a study involving 130 ovarian cancers. They concluded that the initial half-life (cut-off=14 days) and decline profiles were predictive factors of relapse-free survival and overall survival (23). Similar conclusions were reached with the CA125 concentration measured after neoadjuvant chemotherapy (17, 24). The predictive value of the CA125 half-life for the overall survival was reported in patients with ovarian cancer at the end of NAC, but the threshold value varied in different studies (25-28). Tate *et al*. (17) identified the regression coefficient of CA125 as a significant prognostic factor for overall survival (p=0.012). The regression coefficient of CA125 level greater than -0.039 predicts good 3-year survival after subsequent radical surgeries. At this value, the half-time of CA125 level was calculated to be 17.8 days. These mathematical models are complex and difficult to use in routine practice. Makar *et al*. (29) reported that decline of CA125 level to below 65 UI/ml or a reduction of greater than 50% of the pre-NAC level 4 weeks after the 2nd cycle of NAC is an independent prognostic factor for survival. Van Altena *et al*. (19) reported that a CA125 nadir of ≤5 UI/ml is significantly associated with both longer relapse-free survival and longer overall survival (log-rank test p<0.01 and p<0.03, respectively). The CA125 nadir has been reported as an independent prognostic variable (Hazard Ratio=1.51, 95%CI=1.04-2.31) for relapse-free survival. Riedinger *et al*. (23) reported a CA125 nadir threshold of <20 UI/ml. These cohorts comprised of patients in all FIGO stage of disease, who received the standard therapy of epithelial ovarian cancer. In other studies, the predictive value of CA125 normalization after the 2nd cycle was analyzed. Sevelda *et al*. (30) and Redman *et al*. (31) reported an improvement in RFS and OS in case of CA125 level after the 2nd cycle <35 UI/ml. In the other hand, the median follow-up for Sevelda *et al*. was 24 months; and the patients in Redman's study had a mean pre-NAC CA125 level of 321 UI/ml, compared to 2,128 UI/ml in our study.

The results of our study suggest that advanced epithelial ovarian cancer patients who normalized their CA125 level after the 3rd NAC cycle (<35 UI/ml), have significantly longer RFS and OS. Rocconi *et al*. (18) reported similar results. In this study, a correlation was analyzed between the normalization of CA125 by each chemotherapy cycle and the survival. Stage, debulking status, normalization of CA125 by

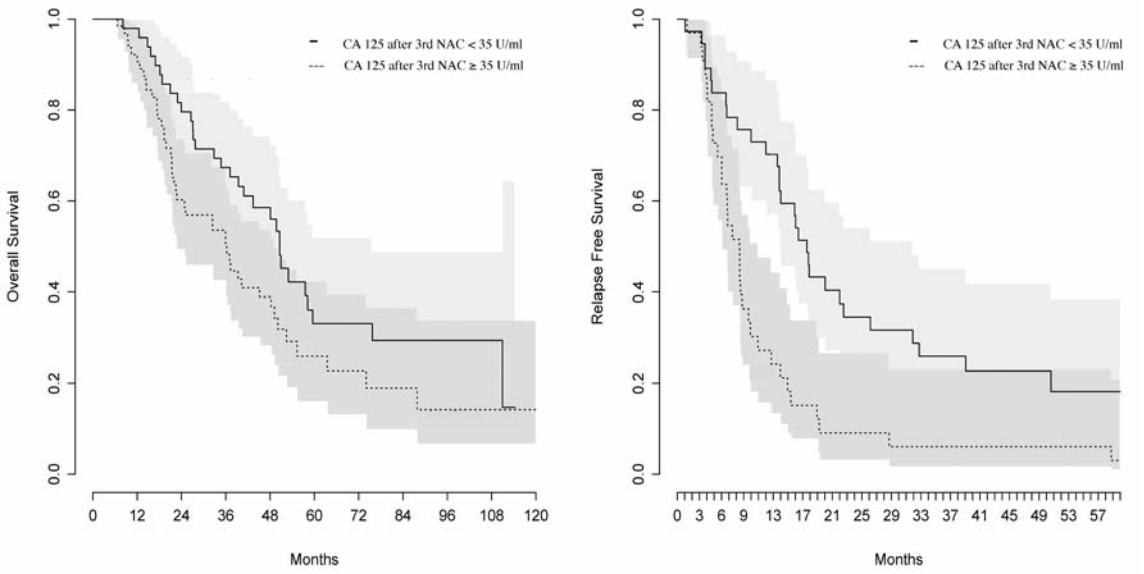

Figure 3. *Kaplan-Meier estimates of the overall and relapse-free survival depending on the CA125 rate after the 3rd NAC. Comparison with the log-rank test (p<0.05).*

the 3rd Cycle (Hazard Ratio=0.57, 95% CI=0.41-0.81) were significantly associated with overall survival in univariate and multivariate analyses.

All these studies suggest the importance of CA125 normalization during NAC to prognosis. Our results confirm that, notably using a logistic regression model and ROC curve can determine the optimal threshold of the most interesting kinetic parameter. The present study is one of the few evaluating the pharmacokinetic parameters of CA125 during neoadjuvant chemotherapy to identify the prognostic factors of platinum sensitivity. The CA125 level after the 3rd NAC cycle seems to be a simple surrogate marker of platinum-sensitivity and was easy to use in our practice. Our findings suggest that patients with a CA125 level after the 3rd NAC cycle that is greater than 35 UI/ml have a high risk of relapse within 12 months and can be considered non-platinum-sensitive. Non-platinum agents may be a more effective alternative to platinum-based regimen in the treatment of patients with partially platinum-sensitive or platinum-resistant disease. Several studies suggest that the use of non-platinum agents, such as pegylated liposomal doxorubicin, topotecan or trabectidin, may help improve the care of this sub-population in relapse (6-11, 32-33). The question may arise regarding the potential benefit to use of these drugs in adjuvant chemotherapy, in case of non-platinum-sensitivity observed during NAC.

Conclusion

In conclusion, we suggest a simple method to evaluate the platinum-sensitivity of epithelial ovarian cancer during neoadjuvant chemotherapy, for early therapeutic adjustment. However, the hypothesis could be confirmed only by additional evidence from prospective studies, before considering the development and evaluation of new treatment protocols for this subset of patients.

Conflicts of Interest

The Authors declare that there is no conflict of interest.

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