Normal serum CA125 half-life and normal serum nadir CA125 level in patients with ovarian cancers

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Summary

The normal serum CA125 half-life and distribution of the normal serum nadir CA125 value in patients with epithelial ovarian carcinoma (EOC) have not been determined yet. Among patients with EOC, 41 patients met the inclusion criteria of the present study: the patients that underwent complete cytoreductive surgery and six cycles of platinum-containing chemotherapy, and who had no recurrent disease more than five years. Serum CA125 half-life ($T_{1/2}$) during primary surgery and primary chemotherapy was calculated and serum nadir CA125 level was evaluated by logarithmic-transformed serum CA125. Median value of nadir CA125 was 7 U/ml (range 3-20 U/ml), and the mean ln (serum nadir CA125) was 1.96 ± 0.45. Mean $T_{1/2}$ was 10.4 days in all patients, and $T_{1/2}$ value was associated with the preoperative serum levels of CA125. Predicted slope of CA125 regression curve was also influenced by the preoperative CA125 value. The present study provides fundamental information with regard to normal half-life time and normal nadir of CA125 in EOC patients.

Key words: Ovarian cancer; CA125; Tumor marker; Half-life; Nadir.

Introduction

Since RECIST (response evaluation criteria in solid tumors) was published in 2000 [1], many clinical studies used these criteria in the assessment of treatment outcomes. In patients with epithelial ovarian carcinoma (EOC), however, many patients develop clinical features of advanced disease such as peritoneal carcinomatosis and advanced disease that are not suitable to be measured by these criteria. Serum level of CA125 is a reliable tumor marker for measuring response, as the marker was elevated in more than 80% of women diagnosed with EOC [2]. CA125 serum concentration is also adopted to evaluate the clinical situation such as response or relapse in EOC patients. In addition, serum CA125 regression during early chemotherapy which is mainly represented by serum half-life seems to be an important predictive and prognostic factor for advanced EOCs [3-10]. On the other hand, the normal CA125 half-life value which was defined as the half-life period observed in cases who achieved optimal cytoreduction and complete remission has not been determined, varying from 4.8 to 12.1 days [4, 5, 11, 12]. These unfixed values might be derived from a small number of the patients analyzed in previous reports (1 to 13 patients), or heterogeneity of the patients. Additionally, it has been reported that the serum nadir CA125 level within normal range (< 35 U/ml) could be a prognostic factor for advanced EOCs [13-16]. However the normal values of serum nadir CA125 and distribution in ovarian cancer patients still remain unresolved. This study was conducted to evaluate the normal serum CA125 half-life and distribution of the normal serum nadir CA125 values during primary surgery and first-line chemotherapy in patients with EOC who underwent complete cytoreductive surgery and achieved completed remission.

Patients and Methods

Between January 1998 and May 2005, 148 patients with EOC were treated with primary cytoreductive surgery (PCS) followed by platinum-based chemotherapy at the National Defense Medical College Hospital. Forty-one patients who met the inclusion criteria were enrolled in this investigation: (a) patients who received no prior chemotherapy before any surgical therapy; (b) patients who underwent macroscopically complete cytoreductive surgery with complete surgical staging including hysterectomy, bilateral salpingo-oophorectomy, peritoneal washing, partial omentectomy, pelvic lymphadenectomy, and paraaortic lymphadenectomy; (c) patients treated with six cycles of platinum-containing chemotherapy after PCS; (d) patients whose serum CA125 levels were more than 35 U/ml; (e) patients who had no recurrent disease more than five years after PCS.

In all cases, a platinum-based combination therapy such as cyclophosphamide and doxorubicin and cisplatin (CAP), etoposide and cisplatin (EP), irinotecan and cisplatin (CPT-P), paclitaxel and carboplatin (TC), and docetaxel and carboplatin (DC), was used for the first-line chemotherapy after PCS. The CAP regimen consisted of 500 mg/m^2 of cyclophosphamide, 50 mg/m^2 of doxorubicin, and 50 mg/m^2 of cisplatin on day 1. The EP regimen consisted of 50 mg/m^2 of etoposide during days 1-5 and 50 mg/m^2 of cisplatin on day 1. The CPT-P regimen consisted of 22.5 mg/m^2 of irinotecan during days 1-5 and 10 mg/m^2 of cisplatin during days 1-5. The TC regimen consisted of 180 mg/m^2 of paclitaxel and AUC = 5 of carboplatin on day 1. The DC regimen consisted of 70 mg/m^2 of docetaxel and

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AUC = 5 of carboplatin on day 1. All regimens were given every three to four weeks. In the present analysis, all regimens were categorized into two groups: "platinum-based therapy" and "taxanes plus platinum". Platinum-based therapy included CAP, EP, and CPT-P regimens, and taxanes plus platinum therapy included TC and DC regimens.

Patients were routinely monitored as follows: month 1 to month 6, physical examination and serum tumor marker estimation including serum CA125 level on the day or one day prior to each cycle of chemotherapy, computed tomography (CT) or magnetic resonance imaging (MRI) every three cycles of chemotherapy; month 7 to year 2, physical examination and serum tumor marker estimation including CA125 every one to two months, CT or MRI every six months; year 3 through year 5, physical examination and serum tumor marker estimation including CA125 every three to five months, CT or MRI annually; year 6 and over, physical examination and serum tumor marker estimation including CA125 annually, CT if indicated. Additional clinical assessments were performed as indicated clinically. For example, CT or MRI were usually recommended when serum CA125 was elevated more than 70 U/ml. The serum tumor marker including CA125 before PCS was obtained within four days before PCS.

Progression of the disease (PD) was defined as the appearance of a new lesion evaluated by a CT of the chest/abdomen or pelvic MRI. The serum levels of tumor markers including CA125 were not used for the definition of PD.

Serum CA125 half-life ($T_{1/2}$) during PCS and primary chemotherapy was calculated according to Buller's formula [12] and Gadducci's formula [7] derived from van der Burg *et al's* report. We set C1 as the serum level of CA125 before PCS, and C2 as the first CA125 level < 35 U/ml, and t1 and t2 as the corresponding time in days; *s* is the slope of the regression of serum CA125.

[1] $s = \ln(C1/C2) / (t2 - t1)$

[2] $T_{1/2} = \ln 2/s$

In addition, we evaluated the correlation between s and ln(C1). The serum nadir CA125 level was also evaluated by logarithmic-transformed serum CA125 to evaluate if these values showed a normal distribution which was observed in healthy women [17].

Statistical analyses were performed using StatMate III software (ATMS Co. Ltd., Tokyo, Japan). Values are shown as mean ± SEM when applicable. Comparisons were evaluated with the Fisher's exact probability test or the chi-square test when appropriate. Parameters were evaluated with the two tailed unpaired Student's *t*-test or compared by one-way analysis of variance (ANOVA). The correlation between s and ln(C1) was analyzed by Pearson's correlation test. The prediction of s from ln(C1) was analyzed by a linear regression test. Values of $p < 0.05$ were considered significant.

Results

A total of 41 EOC patients were enrolled in the present study. The characteristics of patients are shown in Table 1. Median age was 53 years (range: 35-71), and median follow-up period of the cases from PCS was 58 months (range, 65-109 months). Median interval between the date of PCS and the first chemotherapy was 18 days (range: 12-28 days). Twenty-three patients underwent a second-look laparotomy, and pathological complete remission was confirmed.

The number of patients was 24 (59%) in Stage Ic, ten (24%) in Stage II, and seven (17%) in Stage III according to the International Federation of Gynecology and Obstetrics (FIGO) staging methods. Histological subtype was serous type in 12 (29%), endometrioid type in 12 (29%), clear-cell type in 11 (27%), and mucinous type in six cases (15%). Platinum-based therapy was used for 25 cases: 11 cases by CAP, five cases by EP, and nine patients by CPT-P. EP regimen was mainly used five patients with mucinous type, and CPT-P regimen was

Table 1. — *Characteristics of the patients*.

	Number of the patients (%)
	41
Age, years	Median 53 (range:35-71)
< 50	13 (32%)
> 50	28 (68%)
FIGO stage	
Ic	24 (59%)
II	10 (24%)
III	7 (17%)
Histology	
Serous	12 (29%)
Mucinous	6 (15%)
Endometrioid	12 (29%)
Clear-cell	11 (27%)
Residual disease	
No residual disease	32 (78%)
Microscopic residual disease	9 (22%)
Primary chemotherapy	
Platinum-based therapy	25 (61%)
Taxanes plus platinum	16 (39%)
C1 (Preoperative CA125 value), U/ml	
35-100	11 (27%)
100-200	7 (17%)
200-1000	8 (20%)
1000-5000	9 (22%)
5000-	6 (15%)
Follow-up period, months	Median 58 (range: 65-109)

Table 2. — *CA125 half-life time ($T_{1/2}$) according to preoperative serum CA125 values (C1).*

C1, Preoperative CA125 (U/ml)	Number of the patients	Mean $T_{1/2}$ (days)
35-100	11	14.2
100-200	7	12.3
200-1000	8	11.9
1000-5000	9	6.3
5000-	6	6.3
All patients	41	10.4

Table 3. — *Predicted slope of CA125 regression curve (s) and CA125 half-life time ($T_{1/2}$) in ovarian cancer patients*.

CA125 (U/ml)	*s*	$T_{1/2}$ (days)	CA125 percentage reduction/4 weeks
50	0.047	14.8	73%
100	0.058	12.0	80%
200	0.069	10.0	86%
500	0.084	8.3	90%
1000	0.095	7.3	93%
2000	0.106	6.5	95%
5000	0.121	5.7	97%

Table 4. — *The slope of serum CA125 regression curve (s) and preoperative CA125 values (C1) according to clinicopathologic variables*.

Variables	Median C1 (U/ml)	s	*p* value
Age (years)			
< 50	172	0.072 ± 0.036	0.20
> 50	798	0.088 ± 0.038	
FIGO stage			
Ic	178	0.073 ± 0.040	0.08
II	1711	0.106 ± 0.023	
III	356	0.084 ± 0.036	
Histology			
Serous	710	0.081 ± 0.039	0.09
Mucinous	180	0.067 ± 0.021	
Endometrioid	1401	0.105 ± 0.045	
Clear-cell	183	0.071 ± 0.026	
Residual disease			
No residual disease	210	0.079 ± 0.039	0.20
Micro residual disease	1272	0.098 ± 0.029	
Regimen			
Platinum-based therapy	296	0.089 ± 0.040	0.24
Taxans plus platinum	535	0.075 ± 0.033	

Table 5. — *Reported CA125 half-life time ($T_{1/2}$) in the patients with ovarian cancers*.

Author	The patients	Mean $T_{1/2}$ (days)
Canney, *et al*. [11]	Early stage, complete resection (n = 7)	12.1
Buller, *et al*. [12]	Stage III-IV, complete resection (n = 13)	10.4
Yedema, *et al*.. [5]	Stage I-II, no recurrence {van der Burg's formula [3]}	10.7
Yedema, *et al*. [5]	Stage I-II, no recurrence {Buller's formula [12])}	9.8
Gadduci, *et al*. [7]	Stage IIc-IV, optimal surgery = 71% (n = 71)	14
Riedinger, *et al*. [9]	Stage IIc-IV, optimal surgery = 51% (n = 553)	15.8
The present study	Stage Ic-III, complete resection and no recurrence for five years (n = 41)	10.4

used for nine patients with clear-cell type. Sixteen patients were treated with taxanes plus platinum therapy: 12 cases with TC, and four cases with DC regimen.

Mean serum CA125 half-life ($T_{1/2}$) was 10.4 days in all patients (Table 2). $T_{1/2}$ was 14.2 days in the patients with CA125 less than 100 U/ml, 12.3 days in those with CA125 levels of 100-200 U/ml, 11.9 days in those with CA125 levels of 200-1000 U/ml, and 6.3 days in the cases with CA125 more than 5000 U/ml. $T_{1/2}$ value was associated with the preoperative serum levels of CA125.

In the simple linear regression analysis for all patients, it could be expressed as the following equation, s = 0.01617 x ln(C1) – 0.01647 (Figure 1). The correlation between s and ln (C1) showed a significant relationship (r = 0.71, $p < 0.001$). In the simple linear regression analysis for patients with C1 > 100 U/ml, it could be expressed as the following equation, s = 0.01727 x ln(C1) – 0.02456. The correlation between s and ln (C1) also a showed significant relationship when C1 > 100 U/ml (r = 0.65, $p < 0.001$). The predicted slope of CA125 regression curve (s), $T_{1/2}$, and CA125 percentage reduction after four weeks according to preoperative CA125 value are shown in Table 3.

The slope of serum CA125 regression curve (s) and preoperative CA125 (C1) according to clinicaopathologic variables are shown in Table 4. There were no significant relationships between s and clinicopathologic variables of age, FIGO stage, histology, residual disease status, and chemotherapeutic regimen.

The median value of the serum nadir CA125 was 7 U/ml (range, 3-20 U/ml). The distribution of the serum nadir CA125 was not normal shaped (Figure 2A). The distribution of the ln (serum nadir CA125) was normal shaped, and the mean and SD of ln(serum nadir CA125) were 1.96 and 0.45 (Figure 2B).

Discussion

The present study revealed the mean value of serum CA125 half-life ($T_{1/2}$) was 10.4 days in all patients. Notably, $T_{1/2}$ was associated with preoperative serum level of CA125, and the correlation between s and ln (C1) showed significant relationship. A summary of reported $T_{1/2}$ and analyzed patient distribution was shown in Table 5. Canney *et al*. reported mean $T_{1/2}$ was 12.1 days in a cohort of seven patients who had complete resection of early stage tumor [11]. Buller *et al*. showed mean $T_{1/2}$ was 10.4 days among 13 patients with Stage II-IV tumors that had complete resection [12]. Yedema *et al*. reported a mean $T_{1/2}$ of 10.7 days by van den Burg's formula in nine patients who had complete resection of Stage I-II tumors and that of 9.8 days by Buller's formula in five patients with Stage I-II tumors with complete resection [5]. However, these reports were not based on the serum CA125 values before PCS or chemotherapy. We would stress there have been very few reports on the correlation between serum CA125 regression and serum CA125 values before PCS. Peters-Engl *et al*. implied that the patients with low serum CA125 level before chemotherapy would have a low decline in CA125; however, the detailed results were not shown [18]. Reidinger *et al*. evaluated the serum CA125 half-life in only cases with serum CA125 more than 100 U/ml before chemotherapy, and they suggested low CA125 level (< 100 U/ml) before chemotherapy was too low to enable half-life calculations [9]. Our study demonstrates a significant correlation between $T_{1/2}$ and preoperative CA125 values when the serum CA125 > 35 U/ml. Buller *et al*. reported that serum CA125 regression fit the exponential model most, when C1 was set as the level of CA125 before PCS, and C2 as the first CA125 level < 35 U/ml [12]. Yedema *et al*. reported that the cytoreductive surgery itself might cause a transient CA125 rise, so we did not estimate the CA125 values within two weeks after PCS [19]. An investigation during the first-line paclitaxel/platinum chemotherapy showed that patients with the serum CA125 half-life ≤ 14

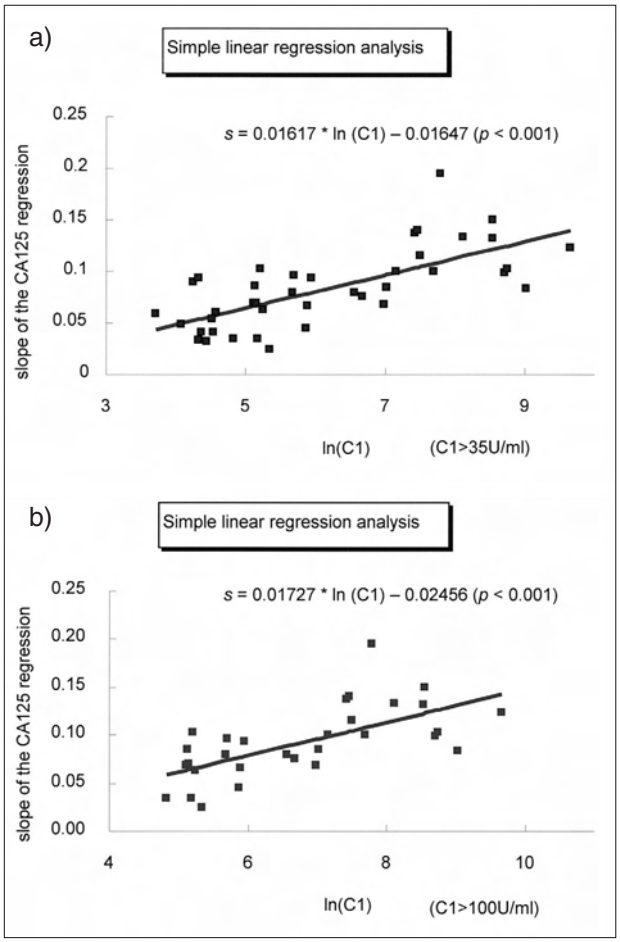

Figure 1. — The correlation between the slope of the regression of serum CA125 (s) and ln[preoperative CA125 value (C1)] in all the patients. The correlation between *s* and ln(C1) showed a significant relationship: r = 0.71, $p < 0.001$. In the simple linear regression analysis, it could be expressed as the following equation, $s = 0.01617 \times \ln(C1) - 0.01647$.

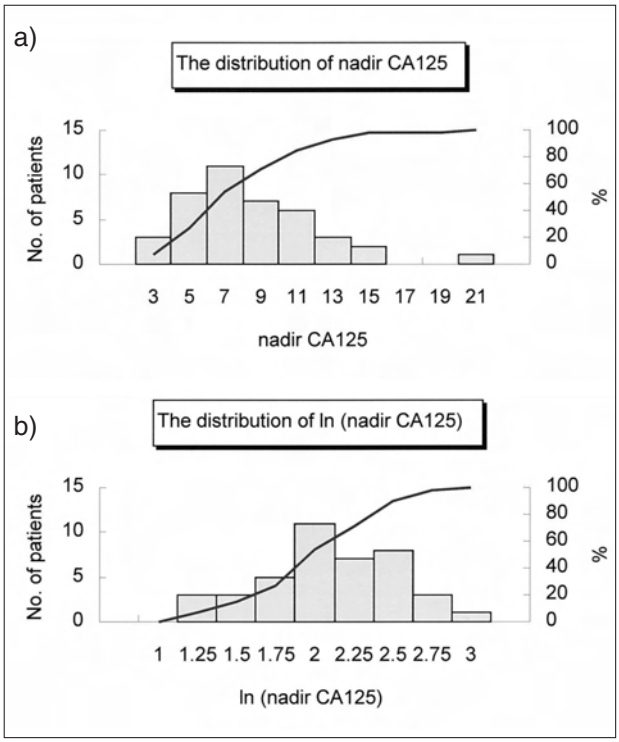

Figure 2. — The distribution of serum nadir CA125 (a) and distribution of ln(serum nadir CA125) (b). The median value of the serum nadir CA125 was 7 U/ml (range, 3-20 U/ml). The distribution of the serum nadir CA125 was not normal shaped. The distribution of the ln(serum nadir CA125) was normal shaped. The mean value of ln(serum nadir CA125) was 1.96 ± 0.45, corresponding to a 95% reference range from 2.9 to 17.3 U/ml.

days and mono-exponential decay had better outcome than patients with that ≤ 14 days and bi-exponential decay [20]. It is assumed that patients with an initially low CA125 had mono-exponential decay. The serum CA125 values cannot have bi-exponential decay to be less than 35 U/ml when the serum CA125 is near to 35 U/ml. The correlation coefficients between the exponential model and serum CA125 regression were very high (r = 0.95-0.98) [9, 12]. Tsuda *et al*. reported that CA125 regression in a paclitaxel-containing regimen was slower than that in a non-paclitaxel regimen [21]. In their report, there was difference of the mean value in initial serum CA125 levels, which might lead to significant difference of CA125 regression by the regimens. The present study clearly suggested the cut-off limit of $T_{1/2}$ was influenced by the CA125 level, and clinical outcome should be evaluated according to the initial values of CA125. Rustin criteria can be superior in a point comparing the effect of the different regimens of chemotherapy, but we have to recognize that it is not suitable in the prediction of individual prognosis of the patients [22]. For further investigation, the normal $T_{1/2}$ obtained by this study would be useful for the assessment of patients with ovarian cancers.

Second, the median value of the serum nadir CA125 was 7 U/ml (range, 3-20 U/ml) in the present study. The distribution of the ln (serum nadir CA125) was normal shaped (95% range, 2.9-17.3 U/ml), as was observed in the distribution of serum CA125 of healthy women [17]. Median serum CA125 value was 14.2 U/ml (95% range, 6.0-41.0 U/ml) in healthy postmenopausal Caucasian women, and 9.0 U/ml (range, 4.0-26.0 U/ml) in African women, and 13.0 U/ml (range, 5.9-33.3 U/ml) in Asian women [17]. The normal serum nadir CA125 values investigated in our study seem to be lower than the reported serum CA125 values of healthy postmenopausal women. This might be explained by the fact that serum CA125 values were influenced by hysterectomy and bilateral salpingo-oophorectomy. Alagoz *et al*. suggested that serum CA125 value of the patient who underwent hysterectomy and bilateral salpingo-oophorectomy (TH/BSO) was lower than that of the normal population [23]. According the report, serum CA125 values of two-thirds of patients treated with TH/BSO were less than 10 U/ml, and 95% of the cases had CA125 levels lower than 20 U/ml. Recently, Santillan *et al*. reported that the medi-

an CA125 nadir level at the time of complete clinical and radiographic response (CR) was 6 U/ml (range, 3-16 U/ml) in the recurrence group, and 11 U/ml (range, 4-17 U/ml) in the non-recurrence group [24]. Markman *et al*. revealed that patients with baseline CA125 values before initiation of maintenance of chemotherapy ≤ 10 U/ml had a superior progression-free survival compared with the cases with higher levels of CA125 [15]. Clinically, the upper limit of the normal serum CA125 values after initial treatment in patients with ovarian cancer is usually defined as 35 U/ml. Our results are in agreement with those reports where the upper limit of the normal serum CA125 values was lower than 20 U/ml. It is possible that the upper limit of normal serum CA125 values is lowered excessively as we determine the recurrence risk after CR only with the serum nadir CA125 value. However, we believe that comprehensive evaluation of the distribution of non-recurrence patients would be most important, although our study had a limitation based on a relatively small number of patients. In addition, the distribution of logarithmic-transformed serum CA125 showed normal shaped more than absolute value of CA125. Further investigation including a large number of cases is necessary to evaluate the clinical usefulness of our results.

Conclusion

The present study provides novel and fundamental information on the normal serum CA125 half-life and distribution of the normal serum nadir CA125 values during first-line chemotherapy in patients with EOC who showed completed remission after primary therapy.

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