CA 125

A Valid Marker in Ovarian Carcinoma Patients Treated with Paclitaxel?

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BACKGROUND. Changes in serum CA 125 from baseline do not reflect response to paclitaxel in relapsed ovarian carcinoma patients. Our study aimed to determine whether CA 125 changes relate to tumor response and overall survival during paclitaxel salvage treatment.

METHODS. Response data and CA 125 values of 77 platinum pretreated ovarian carcinoma patients were included in the study. Patients received 496 courses of paclitaxel in total (median 6; range: 2–18 courses).

RESULTS. Response group numbers on the basis of World Health Organization (WHO) criteria were: 7 partial response, 22 stable disease, and 48 progressive disease. CA 125 values at the moment of clinical response allocation, the median survival duration, and the 3-year survival rate did not differ among WHO defined response groups. For both the stable disease group and the responders, the slopes of the exponential CA 125 regression curves during paclitaxel treatment were negative. Response groups, as defined by CA 125 changes, i.e., halving or doubling of baseline values, after 4 courses were concordant with WHO defined response groups in only 27%, but predicted survival far better.

CONCLUSIONS. This study confirms that CA 125 changes in patients receiving paclitaxel treatment do not correlate with response allocations according to WHO criteria. In particular, patients with clinically and radiologically defined progression will often not show an increase in CA 125 concentrations from baseline. Those patients who do show doubling of CA 125 values, however, have a very poor prognosis. The CA 125 ratio, as determined after 4 courses of paclitaxel treatment, may be a better indicator of response than WHO defined response status. ***Cancer* 1996; 78:118–27.** © *1996 American Cancer Society.*

KEYWORDS: CA 125, paclitaxel, ovarian cancer, chemotherapy, Taxol.

Paclitaxel (Taxol®; Bristol-Myers Squibb Company, Princeton, NJ) is a recent anticancer agent isolated from the bark of the Western Yew (Taxus brevifolia), that is increasingly used in the treatment of ovarian carcinoma, both in platinum-refractory and in platinum-non-refractory disease. Its unique cytotoxic mechanism is based on promotion and stabilization of microtubules.[1] CA 125 antigen serum concentrations have been reported to be an excellent predictor of response not only in patients who are treated with platinum-containing therapy,[2] but also in patients with recurrence or progression of ovarian carcinoma who are treated with paclitaxel.[3–5] Eisenhauer et al.[6] and Pearl et al.,[7] however, reported that changes in CA 125 antigen serum concentrations from baseline did not always enable the response to be predicted correctly.

The purpose of our study is to determine whether or not CA 125 antigen serum concentrations are of any value in assessing tumor

response during paclitaxel salvage treatment of patients with ovarian carcinoma.

PATIENTS AND METHODS

Patients

Between July 1991 and November 1993, 117 patients with progressive or recurrent ovarian carcinoma were treated at the Department of Medical Oncology of The Netherlands Cancer Institute (Antoni van Leeuwenhoek Huis) in a European-Canadian trial evaluating paclitaxel treatment (Bristol-Myers Squibb Company, Wallingford, CT, Protocol no. CA139-015 and CA139-052). Forty-six patients with measurable disease who had previously been treated with either 1 or 2 platinum-containing regimens, were treated in the first protocol, which was a randomized, nonblinded study in which high versus low dose (175 mg/m^2 vs. 135 mg/m^2) and long term versus short term infusion (24 vs. 3-hour continuous infusion) were compared.[6] In a second protocol, a Phase II nonrandomized study, another 71 patients were evaluated. Patients who had been treated with 1 or 2 regimens of platinum-containing chemotherapy received 175 mg/m^2 paclitaxel in a 3-hour continuous infusion and those who had had 3 regimens or more received 135 mg/m^2, also in a 3-hour continuous infusion. Informed consent was obtained from all patients.

Of these 117 patients, 77 were included in the present CA 125 evaluation study. Two patients with cancer of the fallopian tube were excluded, as were three others with incomplete data and three who had received only 1 course of paclitaxel. Thirty-two patients could not be evaluated because of missing serum CA 125 values.

The remaining 77 patients who form the study population had a histologic diagnosis of epithelial ovarian cancer and had been treated with at least two courses of paclitaxel. In total, 496 courses were given (median: 6, range 2–18). Table 1 gives the distribution of courses over the various regimens and response groups. In the absence of toxic effects, the course was repeated every 3 weeks. When a patient developed either hematologic and/or nonhematologic toxic effects, the dose was adjusted. The response to treatment was prospectively evaluated every 2 courses clinically and/or radiologically until the moment the patients could be allocated to 1 of the 4 clinical response groups according to World Health Organization (WHO) criteria, as described by Miller et al.[8] Patients with progressive disease (PD) went off protocol therapy, those who achieved a partial response (PR) continued for 4 courses, or less in the case of relapse or unacceptable toxicity, and those with a complete response (CR) continued for another 4 courses or until they reached unacceptable toxicity. Those who could not be allocated in 1 of these 3 response groups were considered having stable disease (SD) and continued for 6 to 10 courses or until unacceptable toxicity occurred.

CA 125 Assay

Serum CA 125 concentrations were determined before each course with paclitaxel treatment. All blood samples were collected by venipuncture and kept stored at −20 °C until assayed for CA 125. Until March 1993, the CA 125 concentrations were measured using the IRMA-Mat® CA 125 (Byk-Sangtec, Dietzenbach, Germany) and afterwards, using the LIA-Mat® CA 125 II assay (Byk-Sangtec, Dietzenbach, Germany). Both assays showed excellent linearity and there was a good correlation between the assays, as described by Bonfrer et al.[9]

CA 125 Parameters

The following CA 125 parameters were defined and used in the study:

1. CA 125 value at MCRA. This is the CA 125 value as determined at the Moment of Clinical Response Allocation (MCRA).
2. CA 125 ratio at MCRA. This is the CA 125 value at MCRA divided by the baseline CA 125 value (the CA 125 concentration determined directly before the first course of paclitaxel treatment).
3. CA 125 value after 4 courses of paclitaxel treatment. This is the CA 125 value measured after 4 courses of paclitaxel treatment at the time point directly prior to the fifth course. When a patient had <4 courses, the CA 125 value after 2 courses was taken.
4. CA 125 ratio after four courses of paclitaxel treatment. This is the CA 125 ratio measured after 4 courses of paclitaxel treatment at the time point directly prior to the fifth course. When a patient had <4 courses, the CA 125 ratio after 2 courses was taken.

All 4 CA 125 parameters were compared between WHO response groups using the Mann–Whitney U test. Tests were 2-tailed and $P < 0.05$ was considered significant.

CA 125 Exponential Regression Analysis

1. Exponential regression analysis of the CA 125 values in response groups as defined by WHO criteria was performed using the equation ln(serum CA 125) = i + s (days after initiation of treatment), where the y-axis intercept (i) represents the baseline CA 125 secre-

TABLE 1
Patient, Treatment, and CA 125 Characteristics in Relation to Clinical Response Groups as Defined by World Health Organization Criteria

	Partial response n = 7	Stable disease n = 22	Progressive disease n = 48	Total group n = 77
Median number of courses of paclitaxel (range)				
175 mg/m^2 in 24 hours		9 (7–12)	5.5 (2–12)	7 (2–12)
175 mg/m^2 in 3 hours	10	10 (3–11)	4 (2–18)	7.5 (2–18)
135 mg/m^2 in 24 hours	10 (5–15)	5.5 (5–6)	6 (2–9)	6 (2–15)
135 mg/m^2 in 3 hours	9	10 (6–15)	6 (2–12)	6 (2–15)
Age				
median ± SD	59 ± 9	59.5 ± 14	56 ± 11	56 ± 12
range in years	42–72	40–84	33–88	33–88
CA 125 value at MCRA				
median (U/mL)	85	313	253	245
range	15–400	10–900	15–2980	10–2980
CA 125 value: ≤ 35 U/mL	1	3	3	7
> 35 U/mL	6	19	45	70
CA 125 ratio at MCRA				
median	0.50	0.53[a]	1.15[a]	0.87
range	0.04–1.86	0.19–2.50	0.04–5.99	0.04–5.99
CA 125 value after 4 courses				
median (U/mL)	75	123	200	170
range	20–250	10–2110	15–2980	10–2980
CA 125 ratio after 4 courses				
median	0.47	0.52[b]	0.89[b]	0.61
range	0.06–1.25	0.03–1.29	0.02–5.23	0.02–5.23

[a] $P = 0.002$.
[b] $P = 0.015$.
MCRA: Moment of Clinical Response Allocation; SD: stable disease.

ting tumor burden, and the slope of the regression curve (s) represents the response to treatment.[7,10]

2. Exponential regression analysis of the CA 125 values in response groups as defined by CA 125 ratio after 4 courses of paclitaxel treatment.

The regression curves and Pearson product-moment correlation coefficients (r) were calculated using all data points through the MCRA. Differences between the mean slopes of the exponential regression curves (s) were compared using Student's *t* test.

Definition of Response Groups

1. Response groups as defined by WHO criteria.

Tumor response definitions used were based on WHO criteria[8] and are as follows:

Bidimensionally measurable disease

CR was defined as the disappearance of all clinical evidence of tumor, including normalization of the CA 125 value, determined by 2 observations not less than 4 weeks apart.

PR was defined as a ≥50% decrease in the sum of the products of measured lesions, determined by 2 observations not less than 4 weeks apart. No simultaneous increase in the size of any lesion or the appearance of new lesions may occur. Nonmeasurable lesions must remain stable or regress for this category.

SD was defined as a steady state of response less than PR or progression less than PD of at least 4 weeks duration. There may be no appearance of new lesions for this category.

PD was defined as the unequivocal increase of at least 25% in the product of measured lesions. Appearance of significant new lesions will also constitute PD.

Evaluable disease only

CR was defined as the disappearance of all clinical evidence of tumor, including normalization of CA 125 value, determined by 2 observations not less than 4 weeks apart.

PR was defined as an estimated decrease in tumor size of ≥50% determined by 2 observations not less than 4 weeks apart. There may be no appearance of new lesions for this category.

SD was defined as no significant change for at least four weeks. This includes SD with estimated decrease of ≤50%, and lesions with estimated increase ≤25%.

PD was defined as appearance of any new lesions not previously identified or estimated increase of ≥25% in existing lesions.

2. Response groups as defined by CA 125 parameters.

In addition to the classification of patients in re-

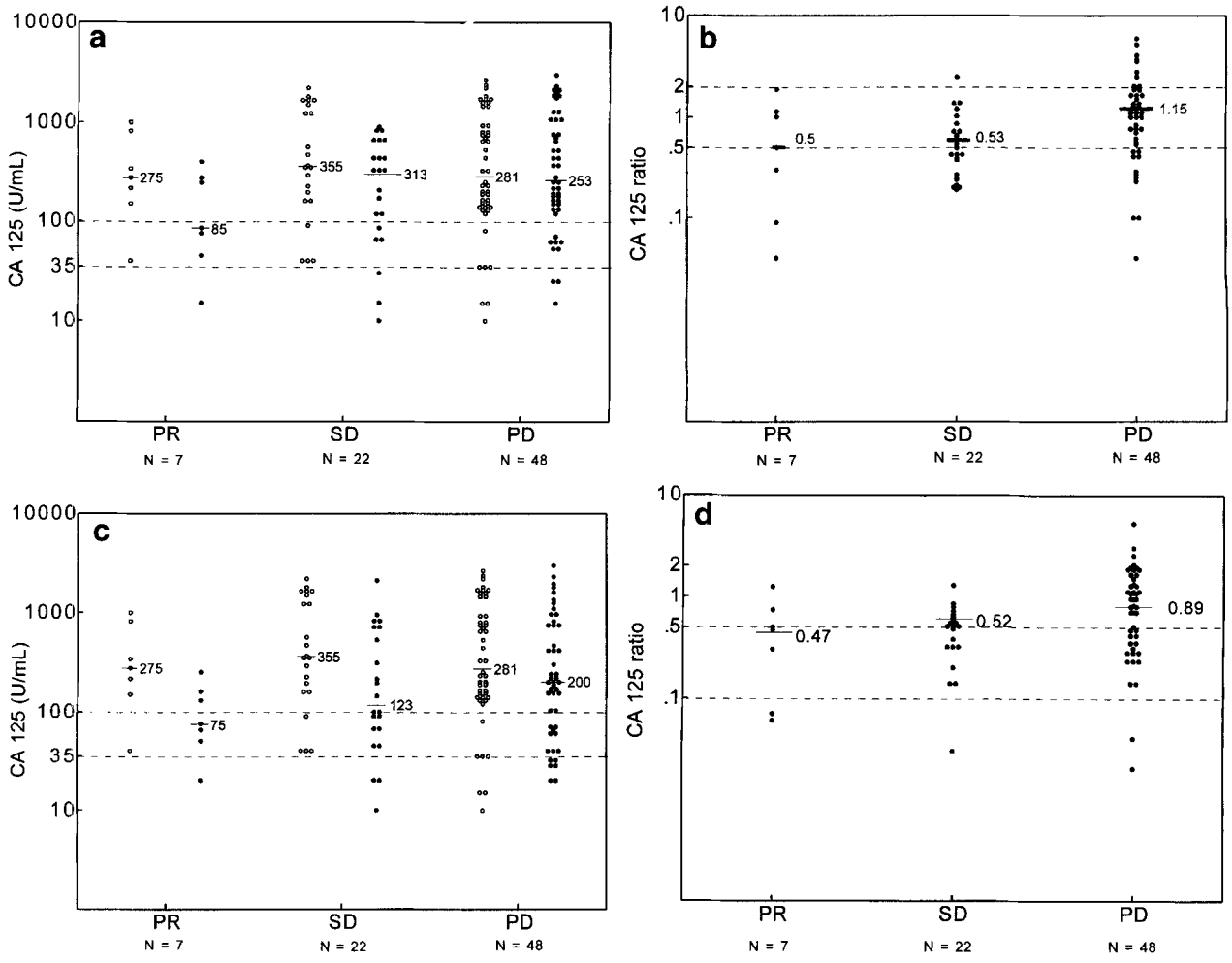


FIGURE 1. (**a**) CA 125 values at the moment of clinical response allocation (MCRA) in clinical response groups as defined by World Health Organization (WHO) criteria: PR: partial response; SD: stable disease; PD: progressive disease; ———: median; -----: CA 125 value of 35 and 100 U/ml; ○: baseline CA 125 value; ●: CA 125 value at MCRA. (**b**) CA 125 ratios at MCRA in clinical response groups as defined by WHO criteria: PR: partial response; SD: stable disease; PD: progressive disease; ———: median; -----: CA 125 ratio of 0.5 and 2.0. (**c**) CA 125 values after 4 courses of paclitaxel in clinical response groups as defined by WHO criteria; PR: partial response; SD: stable disease; PD: progressive disease; ———: median; -----: CA 125 value of 35 and 100 U/ml; ○: baseline CA 125 value; ●: CA 125 value after 4 courses. (**d**) CA 125 ratios after 4 courses of paclitaxel in clinical response groups as defined by WHO criteria; PR: partial response; SD: stable disease; PD: progressive disease; ———: median; -----: CA 125 ratio of 0.5 and 2.

sponse groups based on WHO criteria, another classification was assessed in this study based on the absolute CA 125 values and on CA 125 changes during therapy. Definition of response groups on the basis of CA 125 value (at MCRA, respectively, after 4 courses of paclitaxel treatment) was as follows: response (r) was defined as CA 125 values $\leq$ 35 U/mL, stable disease (SD) as CA 125 values $>$ 35 and $<$100 U/mL, and progression arbitrarily as CA 125 values $\geq$ 100 U/mL at that moment. Definition of response groups on the basis of CA 125 changes (CA 125 ratio at MCRA, respectively, after 4 courses of paclitaxel treatment) was as follows: response was defined as CA 125 ratio $\leq$ 0.5 (meaning at least a halving of the baseline CA 125 over time), as a CA 125 ratio $>$ 0.5 and $<$2.0, and progression as a CA 125 ratio $\geq$ 2.0 (meaning a doubling of the baseline CA 125, or more, over time).

Survival Analysis

Survival was defined as the time from initiation of treatment with paclitaxel until death (from any cause) or until March 1, 1995 when the data analysis was finished and patients were still alive. Actuarial survival curves were constructed from the Kaplan–Meier life table method generated by SPSS Software (SPSS Inc.,

TABLE 2
Concordance between Response Groups Based on CA 125 Parameters in Response Groups as Defined by World Health Organization (WHO) Criteria

	Response groups based on WHO criteria			
Response groups based on CA 125 parameters	Responders n = 7	Stable disease n = 22	Progression n = 48	Total n = 77
CA 125 value at MCRA	1/7 (14%)	3/22 (14%)	39/48 (81%)	43/77 (56%)
CA 125 ratio at MCRA	4/7 (57%)	10/22 (45%)	9/48 (19%)	23/77 (30%)
CA 125 value after 4 courses	1/7 (14%)	6/22 (27%)	34/48 (71%)	41/77 (53%)
CA 125 ratio after 4 courses	5/7 (71%)	12/22 (55%)	4/48 (8%)	21/77 (27%)

MCRA = Moment of Clinical Response Allocation.

Chicago, IL). The differences between the 2 curves were tested using the log rank test.

Both median survival times and 3-year survival rates were derived from actuarial survival curves and the 95% confidence intervals (CI) were calculated for both.

RESULTS

Clinical Response Groups as Defined by WHO Criteria and CA 125 Parameters

Patients were assigned to 3 clinical response groups as defined by WHO criteria: PR (n = 7), SD (n = 22), and PD (n = 48) (Table 1). There were no complete responders. At the time of analysis, the median follow-up duration was 542 days (range: 59–1212 days).

CA 125 values and ratios at MCRA and after 4 courses are presented in Figure 1 and Table 1. CA 125 values and ratios after 2 and 3 courses are similar (data not shown). CA 125 ratios at MCRA (Fig. 1b) and after 4 courses (Fig. 1d) differed between the SD and PD groups ($P = 0.002$ and $P = 0.015$, respectively).

Correlation between response groups as defined by CA 125 parameters and the response groups as defined by WHO criteria is given in Table 2. Serum CA 125 values and ratios at MCRA or after 4 courses, found at the moment patients were allocated to a response group as defined by WHO criteria, did lead to a response group classification with only a minor degree of accordance with the WHO group.

Survival

The median duration of survival after initiation of paclitaxel treatment is given in Table 3a. Remarkably, the median survival of 654 days in the 7 patients with a WHO defined response on paclitaxel treatment is shorter than the median survival (of 761 days) in the 22 patients with SD, as defined by WHO criteria (Table 3a). The 7 responders identified by the CA 125 value $\leq$ 35 U/mL at MCRA do much better than the SD group (>1112 days vs. 458 days) (Table 3a), indicating that CA 125 defined response groups, although different from WHO groups, may have better prognostic significance than WHO groups.

Three-year survival rates are given in Table 3b. Overall three-year survival rate for the whole population is 34.6%. Three-year survival in WHO response groups is highly similar for responders (28.6%) and patients with progression during paclitaxel treatment (29.4%), also casting some doubt on the accuracy of the WHO response classification. The CA 125 ratio after 4 courses allowed identification of 4 patients with progression, who all 4 died within the second year (Table 3b, Fig. 2c).

The actuarial overall survival in response groups as defined by WHO criteria was not significantly different between responders and those with progression (Fig. 2a, $P = 0.570$).

The actuarial overall survival rates in responders and those with progression were also compared in CA 125 parameters-based response groups (Fig. 2b–2c). No significant difference was found between responders and those with progression in response groups defined by the CA 125 value at MCRA (Fig. 2b, $P = 0.265$), nor in response groups as defined by the CA 125 ratio at MCRA and in response groups as defined by CA 125 value at 4 courses of paclitaxel treatment (data not shown), but the actuarial survival between responders and patients with progression as defined by CA 125 ratio after 4 courses of paclitaxel treatment differed significantly ($P = 0.001$, Fig. 2c). Also, when comparing patients with progression to all other patients, a significant difference was found in the actuarial survival ($P = 0.002$, data not shown).

Exponential CA 125 Regression Curves during Paclitaxel Treatment

Mean exponential regression curves in response groups as defined by WHO criteria are given in Figure 3a. Individual curves were calculated for each patient in the

TABLE 3a
Median Survival in Days in Clinical Response Groups as Defined on the Basis of World Health Organization (WHO) Criteria or CA 125 Parameters

Response groups as defined by:	PR	SD	PD	Total group
WHO criteria	654 (372-936)	761[a]	343 (232-454)	542 (363-721)
	n = 7 [2]	n = 22 [11]	n = 48 [15]	n = 77[28]
CA 125 value at MCRA	>1112[a,b]	458 (0-1027)	481 (287-675)	542 (363-721)
	n = 7 [4]	n = 12 [4]	n = 58 [20]	n = 77 [28]
CA 125 ratio at MCRA	662 (414-910)	466 (243-689)	312 (217-407)	542 (363-721)
	n = 25 [10]	n = 42 [15]	n = 10 [3]	n = 77 [28]
CA 125 value at 4 courses	544 (138-950)	458 (82-834)	481 (264-698)	542 (363-721)
	n = 11 [4]	n = 16 [6]	n = 50 [18]	n = 77 [28]
CA 125 ratio at 4 courses	458 (272-644)	761[a]	161 (0-359)	542 (363-721)
	n = 32 [8]	n = 41 [20]	n = 4 [0]	n = 77 [28]

PR: partial response; SD: stable disease; PD: progressive disease; MCRA: Moment of Clinical Response Allocation.
[a] (*) = 95% confidence interval not computable.
[b] ** = > 1112 median survival not yet reached, but greater than 1112 days.
( ): confidence interval; [ ]: patients alive.

TABLE 3b
Three-Year Survival Rates in % in Clinical Response Groups, Defined on Basis of World Health Organization (WHO) Criteria or CA 125 Parameters

Response groups as defined by:	PR	SD	PD	Total group
WHO criteria	28.6 (0-62.1)	46.8 (24.1-69.5)	29.4 (15.9-42.9)	34.6 (23.4-45.8)
	n = 7	n = 22	n = 48	n = 77
CA 125 value at MCRA	57.1 (20.4-93.8)	31.3 (3.9-58.7)	32 (19.1-44.9)	34.6 (23.4-45.8)
	n = 7	n = 12	n = 58	n = 77
CA 125 ratio at MCRA	38.5 (18.7-58.3)	35.3 (20.8-49.8)	30 (1.6-58.4)	34.6 (23.4-45.8)
	n = 25	n = 42	n = 10	n = 77
CA 125 value at 4 courses	36.4 (8-64.8)	37.5 (13.8-61.2)	33.3 (19.2-47.4)	34.6 (23.4-45.8)
	n = 11	n = 16	n = 50	n = 77
CA 125 ratios at 4 courses	24.1 (8.8-39.4)	47.1 (31-63.2)	0 (0-42.5)	34.6 (23.4-45.8)
	n = 32	n = 41	n = 4	n = 77

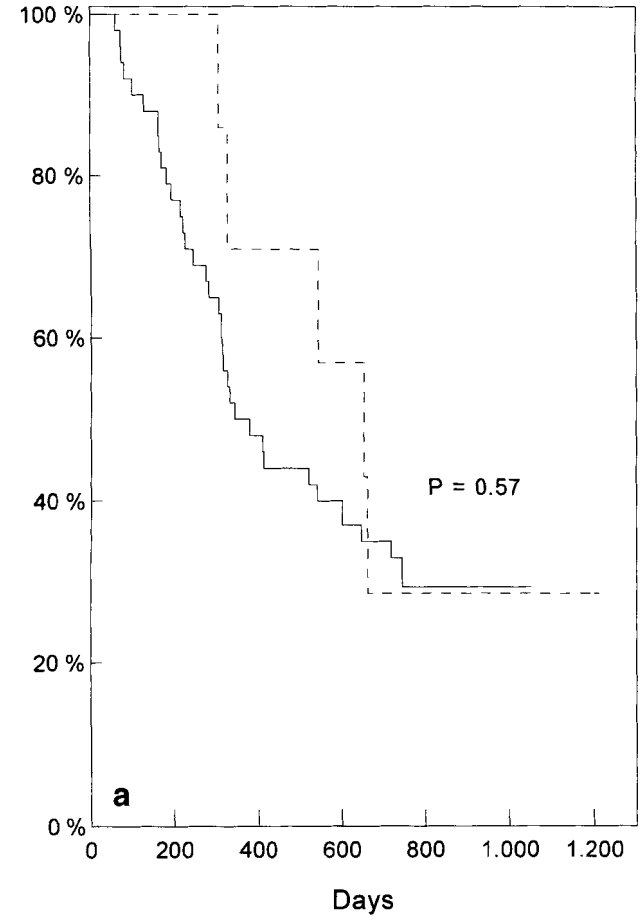
PR: partial response; SD: stable disease; PD: disease; MCRA: Moment of Clinical Response Allocation; ( ) = 95% confidence interval.

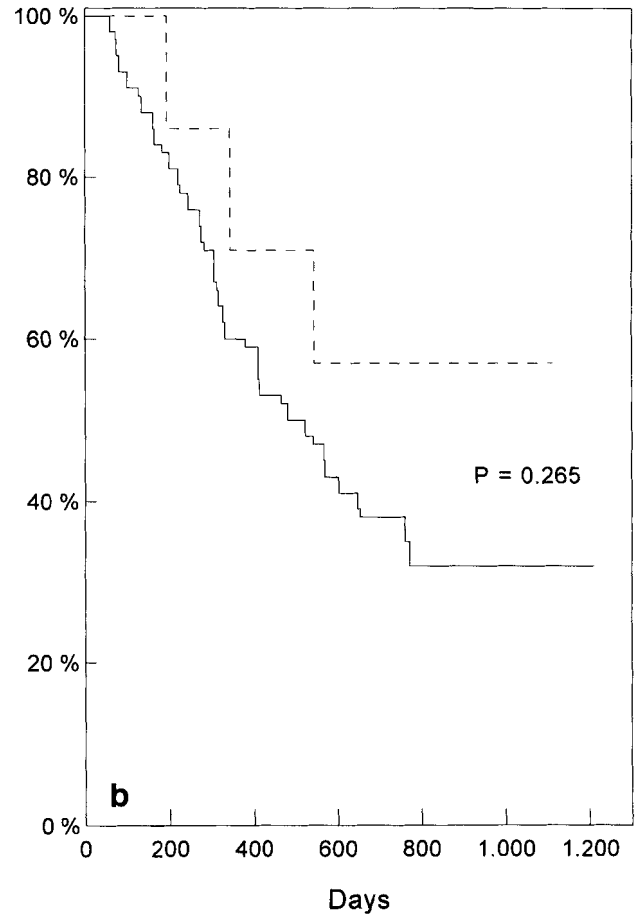
study population. The median number of CA 125 values used for the calculations was 7 (range: 2–19). For the entire study population, the mean slope (s) was −0.0001 (standard deviation (sd) 0.0081), with a y-axis intercept (i) of 5.47 (sd 1.34) and the correlation coefficient (r) being 0.60 (sd 0.29). The clinical utility of the CA 125 exponential regression curve was evaluated by stratifying the study population according to response to treatment. The mean values for s, i, and r for these groups are given in Table 4. The positive slope of the regression curve for patients with progression was significantly different from the negative slopes for patients that responded to paclitaxel treatment ($P = 0.044$) and the SD group ($P < 0.0001$). There was no significant difference between PR and SD ($P = 0.787$).

Mean exponential CA 125 regression curves during paclitaxel treatment in response groups as defined by CA 125 ratio after 4 courses are given in Figure 3b. The mean values for s, i, and r for these groups are given in Table 4. The positive slope of the regression curve for patients with progression was significantly different from the negative slope of the regression curve of patients that responded to paclitaxel treatment ($P = 0.004$), but not from the neutral slope of the SD regression curve ($P = 0.052$). There was a significant difference between the slopes of the curves of the SD group and the response group ($P < 0.0001$).

DISCUSSION

This study, looking at changes in the serum concentrations of CA 125 as a reaction to paclitaxel treatment





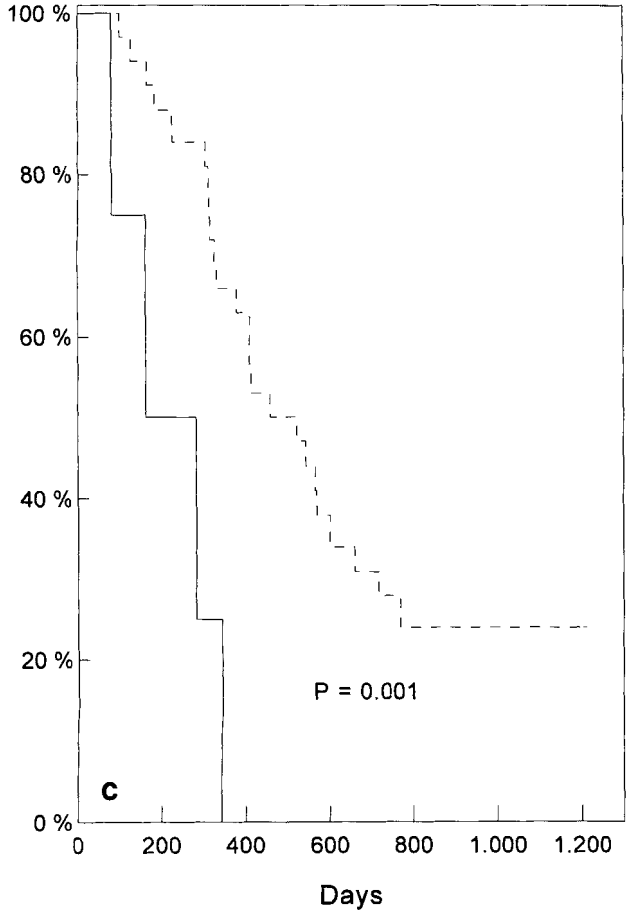


FIGURE 2. (**a**) Actuarial survival in the responders group versus the progression group in clinical response groups as defined by World Health Organization criteria ($P = 0.570$): -----: responders group (n = 7); ———: progression group (n = 48). (**b**) Actuarial survival in the responders group versus the progression group in response groups as defined by CA 125 value at the moment of clinical response ($P = 0.265$); -----: responders allocation group with a CA 125 value $\leq$ 35 U/ml (n = 7); ———: progression group with CA 125 value $\geq$ 100 U/ml (n = 58). (**c**) Actuarial survival in the responders group versus the progression group in response groups as defined by CA 125 ratio after 4 courses of paclitaxel ($P = 0.001$); -----: responders group with CA 125 ratio $\leq$ 0.5 (n = 32); ———: progression group with CA 125 ratio $\geq$ 2.0 (n = 4).

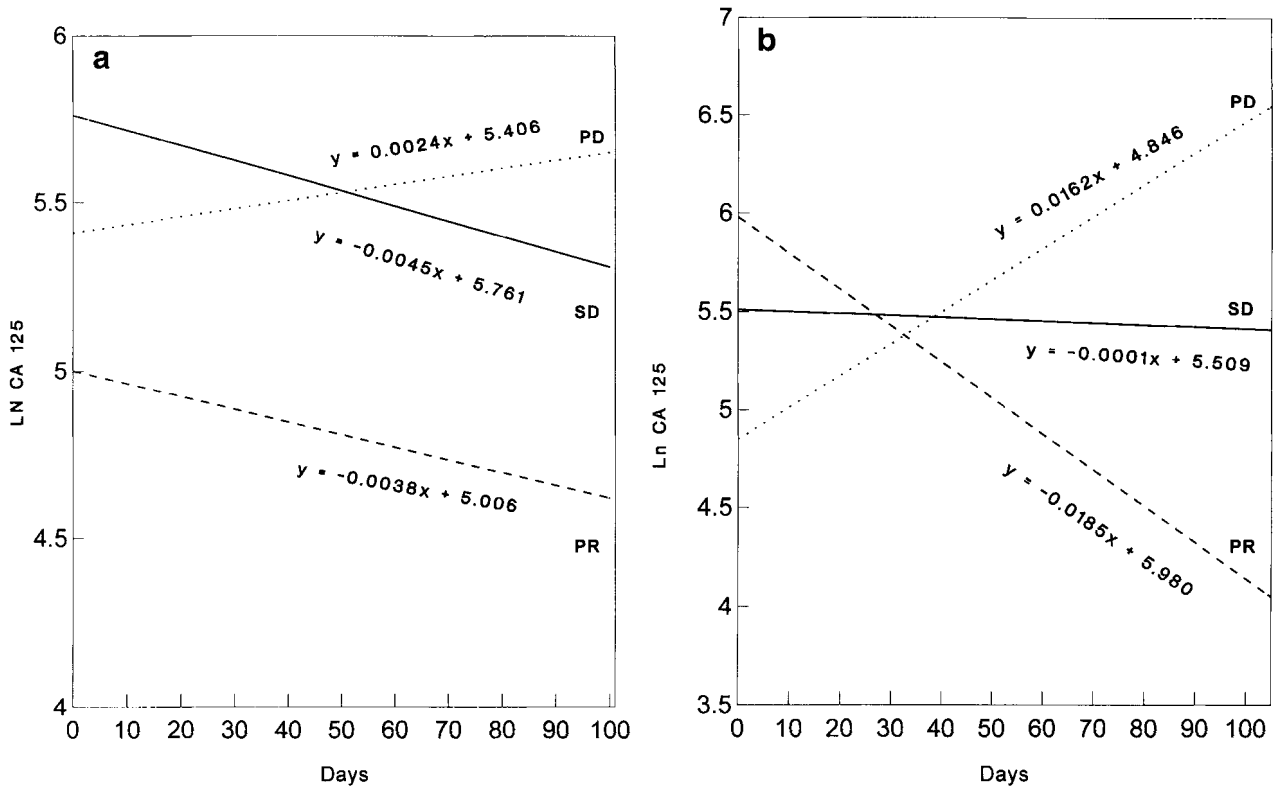


FIGURE 3. (**a**) Exponential regression curves of CA 125 values under paclitaxel in response groups as defined by WHO criteria; -----: responders group (n = 7); ———: stable disease group (n = 22); .....: progression group (n = 48). (**b**) Exponential regression curves of CA 125 values in response groups as defined by CA 125 ratio after 4 courses of paclitaxel: -----: responders group with a CA 125 ratio ≤ 0.5 (n = 32); ———: stable disease group with a CA 125 ratio between 0.51 and 1.99 (n = 41); .....: progression group with a CA 125 ratio ≥ 2.0 (n = 4).

TABLE 4
Mean Values for s, i, and r in Exponential Regression Curves in Response Groups as Defined by World Health Organization (WHO) Criteria and the CA 125 Ratio after Four Courses of Paclitaxel

	Total	s (mean ± SD)	i (mean ± SD)	r (mean ± SD)	*P* value of s
Response groups as defined by WHO criteria					
PR	7	−0.0038 ± 0.0062	5.006 ± 0.781	0.5124 ± 0.2954	PR-SD 0.787
SD	22	−0.0045 ± 0.0038	5.761 ± 1.363	0.6380 ± 0.2455	SD-PD < 0.0001
PD	48	0.0024 ± 0.0088	5.406 ± 1.390	0.5904 ± 0.3045	PD-PR 0.044
Response groups as defined on basis of the CA 125 ratio after 4 courses					
Responders	32	−0.0185 ± 0.0112	5.980 ± 1.602	0.8631 ± 0.1570	PR-SD < 0.0001
Stable disease	41	−0.0001 ± 0.0081	5.509 ± 1.328	0.6502 ± 0.3036	SD-PD 0.052
Progression	4	0.0162 ± 0.0107	4.846 ± 1.868	0.9170 ± 0.1051	PD-PR 0.004

S: mean slope; .: y-axis intercept; r: correlation coefficient; PR: partial response; SD: stable disease; PD: progressive disease.

in relapsed ovarian cancer patients, has 2 equally important findings.

First, CA 125 values and changes therein under paclitaxel treatment, do not correlate very well with response groups to which patients were allocated on the basis of generally accepted WHO criteria (Table 2). Thus, CA 125 does not seem to have any predictive value as to response under paclitaxel treatment. Second, CA 125 parameters correlate better with survival than WHO classification, as shown by actuarial sur-

vival (Fig. 2), median duration of survival (Table 3a) and 3-year survival rate (Table 3b). Doubling or halving of the baseline CA 125 value determined after 4 courses of paclitaxel treatment is a better predictor of final outcome than the clinically and/or radiologically defined response.

Seeing these differences, one might ask how much of a gold standard is provided by the WHO response group classification and how far CA 125 changes under paclitaxel treatment can be neglected in the management of these relapsed ovarian cancer patients.

When treated with paclitaxel, females with relapsed platinum refractory ovarian cancer have a 30% risk of febrile neutropenia and a 20% chance of response (with a relative short duration of remission) and an overall 1-year survival rate of <50%.[11] These factors, and the fact that the drug is expensive with a limited availability, make it very important to be able to rely on accurate response criteria to determine precisely the efficacy of paclitaxel treatment in a given patient undergoing this palliative therapy.

Because the reliability of the relatively cheap CA 125 serum marker (as an indicator of response under paclitaxel treatment) has been questioned,[6,7] many clinicians now use expensive imaging methods like, computed tomography (CT) scan and nuclear magnetic resonance to assess tumor response in these patients.

The present study finds that CA 125 changes lead to response classifications, that are only for 27 to 30% (Table 2) in concordance with the well-known response groups defined by WHO criteria. Similar findings have been reported by others.[6,7]

CA 125 values followed an exponential regression as has been reported for patients undergoing primary therapy.[10,12,13] The regression rate was significantly different in patients with progression from those who showed response or SD as defined by WHO criteria. In the group with progression, the slope of the regression curve was positive, indicating a steady rise in serum CA 125 concentrations. Various studies[10,12,13] showed that a positive regression rate within 60 days is indicative for progression during chemotherapy. The slope of the regression curve was negative and highly similar for those patients with either SD or R to paclitaxel treatment, indicating a fall in serum CA 125 concentrations. We found no significant difference between these last two groups, which indicates that a negative regression rate is of minimal use in distinguishing patients with SD from patients with R to paclitaxel treatment, confirming the study results of Pearl et al.[7] However, from a practical point of view, it is only important to identify patients with progression on therapy, as all others will continue paclitaxel treatment.

All 4 patients in the PD group as defined by CA 125 ratio after 4 courses had also progressive disease according to WHO criteria. However, 44 of 48 patients with clinically and/or radiologically found progression (mostly of intraabdominal disease) had a CA 125 ratio at 4 courses < 2. This is in agreement with the concept that CA 125 antigen shedding in the circulation is less than could be expected on the basis of the increase in tumor volume. The explanation for this phenomenon is still lacking, especially since Bonfrer et al.[14] showed that CA 125 values under paclitaxel treatment, in in vitro conditions, correlated significantly with increasing and decreasing numbers of cancer cells.

In conclusion, serum CA 125 concentration is clinically indeed a weak indicator of response to paclitaxel treatment, when using the WHO response classification as the gold standard. However, when taking survival as the ultimate goal of treatment, it appears that WHO defined response groups themselves are either poorly related or not related to survival. This is strange, as it can be argued that after platinum and paclitaxel regimens, no other form of treatment could modify patients' survival changes substantially. Remarkably, changes in CA 125 values when measured after 4 courses of paclitaxel treatment, do predict survival better or at least as well as WHO groups.

Given that the reliability of the WHO classification could be questioned, with respect to determining the efficacy of paclitaxel treatment, the CA 125 marker seems to be a more reliable, cheaper, and less stressful indicator of lack of response in patients undergoing palliative paclitaxel treatment.

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