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Exponential Regression of CA 125 during Salvage Treatment of Ovarian Cancer with Taxol

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The role of serum CA 125 in monitoring the response of epithelial ovarian cancer to treatment has been extensively investigated. The exponential regression curve [$\ln(\text{CA } 125) = i + s$ (days after initiation of treatment)] has been reported to describe the rate of change of serum CA 125 during treatment. In this model, the *y*-axis intercept (i) represents the initial CA 125-secreting tumor burden, while the slope (s) is determined by the response to treatment. The exponential regression curve was calculated for 66 patients undergoing salvage chemotherapy with taxol. At a mean follow-up of 121 days, 50 (75%) patients had progressed and 35 (53%) had died. Stratification of the patients by stage, grade, or histology did not reveal any significant differences in the regression rate. When the patients were stratified by response, the mean regression rate was 0.0157 ± 0.011 for patients with progressive disease ($N = 19$) vs −0.0250 ± 0.031 for those with stable disease ($N = 25$) and −0.0250 ± 0.015 for those with a partial response ($N = 22$) ($P < 0.0001$). The regression rate did not correlate with progression-free interval or survival ($P > 0.05$). We conclude that changes in serum CA 125 levels follow an exponential regression curve in patients undergoing salvage chemotherapy with taxol for progressive or recurrent ovarian cancer. A positive regression rate may predict which patients will progress prior to the time progression becomes clinically evident. However, a negative rate fails to provide discriminatory utility in predicting progression-free interval or survival.

INTRODUCTION

Ovarian cancer is the fourth leading cause of cancer-related mortality in American women, accounting for approximately 12,500 deaths annually [1]. Although cytoreductive surgery followed by intensive combination chemotherapy has produced clinical response rates of 40–60% [2], 80% will recur within 3 years [3,4]. Early detection of tumor recurrence or progression has remained a challenge, rendering it difficult to determine the appropriate duration of chemotherapy. The development of a radioimmunoassay [5] utilizing a monoclonal antibody (OC 125) against the serum antigen CA 125 has proven valuable in monitoring treatment response in many patients with ovarian cancer.

Numerous investigators have attempted to correlate changes in CA 125 levels with response to treatment [6–8]. Recently, the rate of decline of CA 125 in primarily treated patients with ovarian cancer was reported to follow an exponential regression [9]. Divergence from an ideal regression curve, which could be determined within 60 days of initiation of treatment, uniformly predicted cancer progression. It was suggested that treatment regimens be evaluated based on the regression rate relative to the ideal regression curve.

The primary goals of this study were (1) to determine if the change in serum CA 125 levels followed an exponential regression model in patients undergoing salvage chemotherapy for recurrent or progressive CA 125-secreting ovarian carcinoma, (2) to determine if prognostic factors such as stage, grade, and histology correlated with the regression rate, (3) to investigate the correlation between response to salvage chemotherapy and the regression rate, and (4) to determine if the regression rate had predictive value for progression-free interval and/or survival.

PATIENTS AND METHODS

From June 1991 to January 1993, 98 patients with progressive or recurrent ovarian carcinoma were treated by

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the Division of Gynecologic Oncology at the University of Michigan Medical Center on a National Cancer Institute protocol (TRC-9103) evaluating taxol as salvage therapy. All patients had a histological diagnosis of epithelial ovarian carcinoma and had failed at least two prior chemotherapy regimens, including a platinum-based regimen.

Twenty-nine patients who could not be evaluated by serial serum CA 125 levels were excluded from analysis for this study. Nine patients were marker negative. Twenty patients had only a single CA 125 level measured, each of whom was removed from the study or died of carcinoma prior to receiving a second cycle. The remaining 69 patients form the study population.

All patients were treated with taxol at an initial dose of 135 mg/m^2 given as a 24-hr intravenous infusion. A CA 125 level was measured prior to initiation of therapy and then upon admission for each treatment cycle. In the absence of toxicity, the cycle was repeated every 3 weeks. If significant toxicity occurred, subsequent doses were modified according to the research protocol. The response to treatment was classified according to standard definitions [10]. The progression-free interval was calculated from initiation of treatment with taxol to the time of first objective measurement of disease progression. Survival was measured from initiation of treatment with taxol until death.

Exponential regression analysis of the serum CA 125 levels was performed using the equation

$$\ln(\text{serum CA 125}) = i + s\,(\text{days after initiation of treatment}),$$

where the y-axis intercept (i) represents the initial CA 125-secreting tumor burden, and the slope of the regression curve (s) represents the response to treatment [9]. The regression curves and Pearson product–moment correlation coefficients (r) were calculated using all data points through the first normal CA 125 level. For the patients whose serum CA 125 never normalized, the regression curves and correlation coefficients were calculated using all data points up to the first increase in serum CA 125.

The mean slopes of the regression curves (s), y-axis intercepts (i), and correlation coefficients (r) were compared using the Student t test or one-way ANOVA as appropriate. Actuarial progression-free interval and survival rates were calculated using the Kaplan–Meier life table method [11]. The actuarial rates were compared using the Wilcoxon log-rank analysis. The relationship between the exponential regression rate and the progression-free interval or survival was analyzed with the Spearman rank correlation coefficient. Tests were two-tailed and $P < 0.05$ was considered significant.

TABLE 1
Demographic Information (66 Patients)

Age at treatment (years, mean and range)	58.0 (32–80)
Follow-up (days, mean and range)	121 (21–492)
Deaths[a]	35
FIGO stage	
IA–C	2
IIA–C	4
IIIA–C	50
IV	9
Unstaged	1
Grade	
1	0
2	23
3	41
Undifferentiated	2
Histologic type	
Serous	30
Mucinous	0
Endometrioid	25
Clear cell	8
Undifferentiated	3

[a] All deaths were cancer-related.

RESULTS

Demographic data of the study population are summarized in Table 1. Patients received a median of five cycles of taxol (range 2–15). Twenty-two patients (33%) achieved a partial response to therapy. There were no complete clinical responses. Twenty-five patients (38%) had stable disease, and 19 (29%) patients had progressive disease without an initial response.

The actuarial progression-free interval is presented in Figs. 1 and 2. The median progression-free interval for the entire study population was 98 days (95% CI; 83, 136 days). The median time to progression was 69 days (95% CI; 45, 91 days) for patients with progressive disease, 91 days (95% CI; 65, 135 days) for patients with stable disease, and 205 days (95% CI; 154, 269 days) for those with a partial response. The progression-free interval for patients with a partial response was significantly longer than that for patients with progressive ($P < 0.005$) or stable ($P < 0.005$) disease. There were no significant differences in progression-free interval for the patients with progressive or stable disease.

The actuarial survival is presented in Figs. 1 and 3. The median survival for the entire study population was 232 days (95% CI; 177, 313 days). The median survival was 202 days (95% CI; 81, 346 days) for patients with progressive disease, 161 days (95% CI; 126, 202) for those with stable disease, and 410 days (95% CI; 348, 544 days)

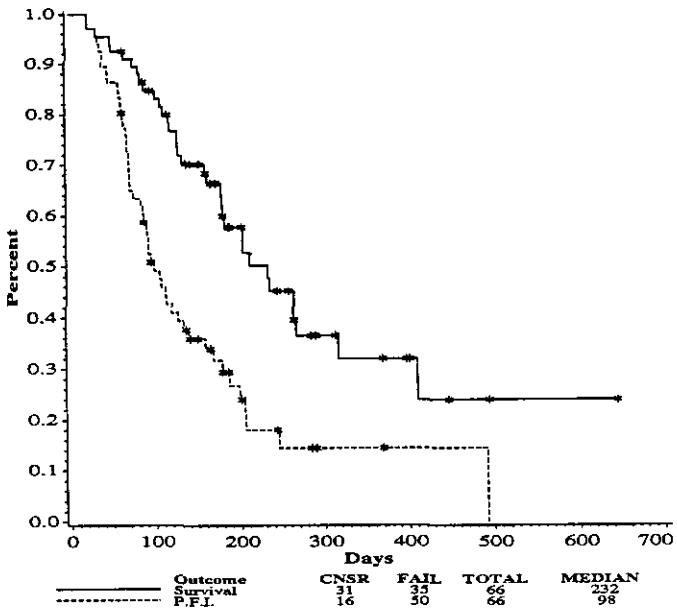

FIG. 1. Actuarial survival (solid line) and progression-free interval (dashed line) for patients with ovarian cancer undergoing salvage chemotherapy with taxol (CNSR, censored).

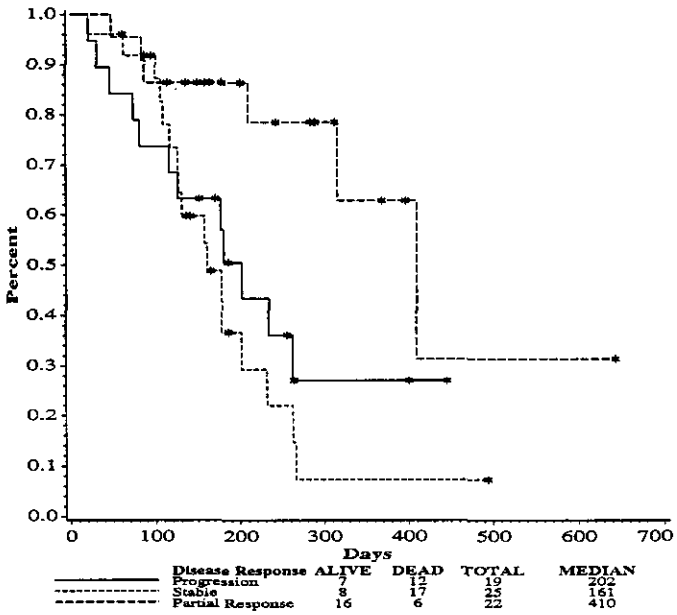

FIG. 3. Actuarial survival of patients with a partial response (long-dashed line), stable disease (short-dashed line), or progressive disease (solid line).

for those with a partial response. The survival for patients with a partial response was significantly longer than that for patients with progressive ($P < 0.05$) or stable ($P < 0.01$) disease. There were no significant differences in survival for the patients with progressive or stable disease.

Mean exponential regression curves for patients with progressive, stable, or partially responsive disease are presented in Fig. 4. Individual curves were calculated for each patient in the study population. The median number of CA 125 measurements used for the calculations was

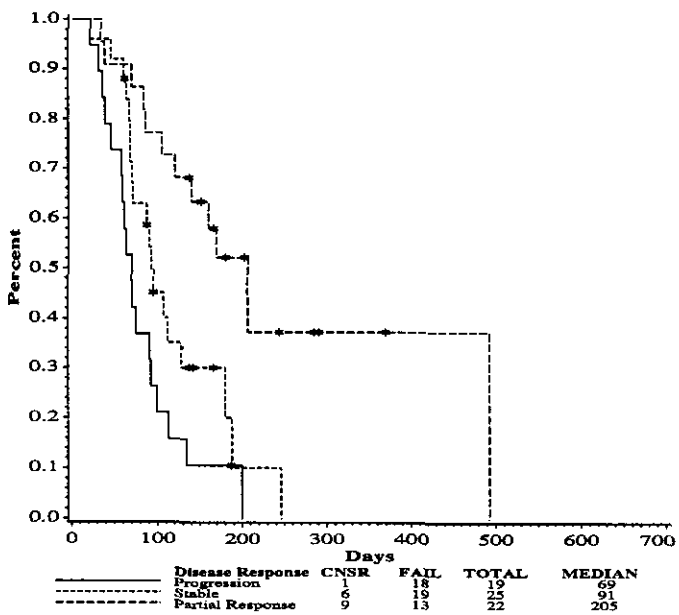

FIG. 2. Actuarial progression-free interval of patients with a partial response (long-dashed line), stable disease (short-dashed line), or progressive disease (solid line) (CNSR, censored).

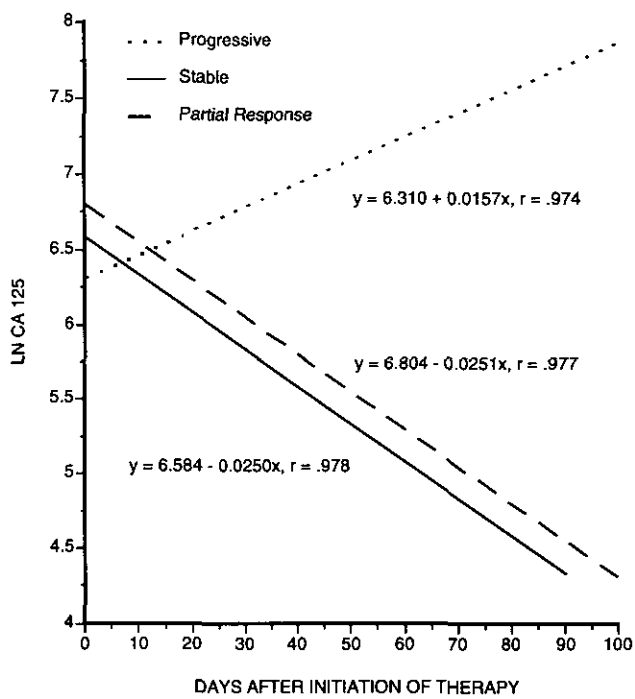

FIG. 4. Mean exponential regression curves for patients with a partial response (dashed line), stable disease (solid line), and progressive disease (dotted line).

TABLE 2
Influence of Stage, Grade, Histology, and Response on *s* and *i*

Factor	*N*	*s* (mean ± SD)	*i* (mean ± SD)
Stage			
I/II	6	0.0000 ± 0.013	6.385 ± 1.904
III	50	−0.0171 ± 0.030	6.741 ± 1.312
IV	10	−0.0026 ± 0.017	5.948 ± 1.146
Grade			
2	23	−0.0163 ± 0.038	6.276 ± 1.265
3	41	−0.0111 ± 0.022	6.726 ± 1.417
Undifferentiated	2	−0.0225 ± 0.013	7.364 ± 0.235
Histology			
Serous	30	−0.0089 ± 0.019	6.935 ± 1.271
Endometrioid	25	−0.0213 ± 0.037	6.017 ± 1.266
CC	8	−0.0024 ± 0.025	6.629 ± 1.788
Undifferentiated	3	−0.0197 ± 0.011	6.549 ± 1.421
Response			
Progressive	20	0.0157 ± 0.011[a]	6.310 ± 1.434
Stable	26	−0.0250 ± 0.031	6.584 ± 1.128
Partial response	23	−0.0250 ± 0.015	6.804 ± 1.493

[a] $P < 0.0001$ vs stable or partial response.

4 (range 2–8). For the entire study population, the mean slope (*s*) was 0.0126 (95% CI; −0.006, −0.018), the *y*-intercept (*i*) was 6.475 (95% CI; 6.134, 6.819), and the correlation coefficient (*r*) was 0.980 (95% CI; 0.973, 0.988). There were no significant differences in *s*, *i*, or *r* when the patients who had only two CA 125 levels measured were excluded (data not shown).

The impact of various prognostic factors on the regression curve was evaluated by stratifying the study population according to stage, grade, and histology. The mean values for *s* and *i* for these groups are presented in Table 2. There were no significant differences in either *s* or *i* among stages or histology, nor in *s* among grades.

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* and *i* for these groups are presented in Table 2. The slope of the regression curve for patients with progressive disease was significantly different than that for patients with stable ($P < 0.0001$) or partially responsive ($P < 0.0001$) disease. There were no significant differences in *s* for patients with stable and partially responsive disease, nor in *i* among any of the groups.

The relationship between the CA 125 exponential regression rate and the progression-free interval or survival was analyzed with the Spearman rank correlation coefficient. The rate of regression was correlated with neither the progression-free interval ($P = 0.0589$) nor survival ($P = 0.919$), although the correlation approached statistical significance for the progression-free interval.

DISCUSSION

The results of this study suggest that the rate at which serum CA 125 levels change can provide valuable information about the response to salvage chemotherapy in patients with recurrent or progressive ovarian cancer. The rate of change for patients in the present study followed an exponential regression, as has been reported for patients undergoing primary therapy [9].

Although stage, grade, and histology have been considered important prognostic factors in patients undergoing primary therapy [12,13], there were no significant differences in the regression rate when the patients in the present study were stratified according to these factors. This is a manifestation of the principle that malignancies do not respond as well to salvage as to primary therapy [14]. Thus, in this population of heavily pretreated patients, the overriding prognostic factor becomes previous exposure to chemotherapy, with the development of induced (e.g., expression of the multidrug resistance gene MDR-1) [15] or spontaneous drug resistance [16].

The regression rate was significantly different for patients who failed to demonstrate any response to treatment from that for those whose disease was initially stable or partially responsive. In the former group, the slope of the regression curve was positive, indicating a steady rise in serum CA 125 levels. Data from previous studies have demonstrated that a rise in the serum CA 125 level precedes clinical evidence of progression by several months in patients with ovarian cancer known to secrete

CA 125 [17,18]. Therefore, a positive regression rate, which can be calculated within 60 days [9], could indicate which patients will progress despite chemotherapy with taxol. These patients might be switched to an alternative regimen without waiting for clinical evidence of progression.

In contrast, the slope of the regression curve was negative for those patients with either stable or partially responsive disease, indicating a fall in serum CA 125 levels. However, the regression rate was not significantly different between these two groups, suggesting that a negative regression rate is of minimal clinical utility for distinguishing the degree of response to taxol. This is further supported by the lack of correlation between the regression rate and either progression-free interval or survival for these two groups. One hypothesis for this lack of correlation is that taxol selectively kills CA 125-secreting cells.

It is clear from previous studies that changes in serum CA 125 levels are more accurate for making positive rather than negative predictions regarding prognosis [7,8,19]. Failure of serum CA 125 to reach normal levels or to fall at a given rate indicates a very high probability of residual disease following cytoreductive surgery [20] or at second-look laparotomy [17]. In addition, over 50% of patients with normal serum CA 125 levels and a negative clinical evaluation will have persistent disease at second-look laparotomy [21].

In conclusion, the results of this study demonstrate that changes in serum CA 125 levels follow an exponential regression curve in patients undergoing salvage chemotherapy with taxol for progressive or recurrent CA 125-secreting ovarian cancer. A positive regression rate may predict which patients will progress prior to the time progression becomes clinically evident. However, a negative rate fails to provide discriminatory utility in predicting progression-free interval or survival.

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