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Predictive value of serum CA-125 levels in patients with persistent or recurrent epithelial ovarian cancer or peritoneal cancer treated with bevacizumab on a Gynecologic Oncology Group phase II trial

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Abstract

Purpose—To compare two methods of determining therapeutic response and disease progression - modified Gynecologic Cancer Intergroup (GCIG) criteria based on CA-125 and Radiographic Evaluation Criteria in Solid Tumors (RECIST), in a phase II trial of bevacizumab for patients with recurrent or persistent epithelial ovarian and peritoneal carcinoma.)

Patients and Methods—Patients were treated with bevacizumab 15 mg/kg every 21 days. Modified GCIG definitions of progression and response were retrospectively applied and compared to RECIST-defined progression and response. The prognostic significance of CA-125- and RECIST-defined responses and progressions were explored.

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These results were presented at the 2009 Joint Annual Meetings of the Western Association of Gynecologic Oncologists and the Society of Gynecologic Oncology of Canada, June 2009.

CONFLICT OF INTEREST

Dr. Robert Burger served as a consultant for Genentech/Roche, but has not been compensated for this activity. All other co-authors have no conflict of interest to declare.

Results—Sixty-two patients were evaluable by RECIST, 59 for progression by CA-125, and 45 for response by CA-125. Median progression-free survival (PFS) by RECIST and progression-free interval (PFI) by CA-125 were 4.7 and 5.2 months respectively. However, 12.9% of those with CA-125 defined progression remained progression-free according to RECIST for at least 8 months. Thirteen of 62 patients (21%) had response by RECIST and 14/45 (31%) by CA-125. Time dependent analyses indicated that progression by CA-125 was associated with a 5.2 fold increased risk of progression by RECIST, and response by CA-125 had a 5 fold decrease in risk of progression by RECIST. Landmark and time dependent analyses showed prognostic value of responses by CA-125 and RECIST.

Conclusions—In this study, disease assessment by RECIST and CA-125 appear to correlate in general. However, approximately 10% of patients might demonstrate progression earlier by CA-125.

INTRODUCTION

In clinical trials for solid tumors, National Cancer Institute Response Evaluation Criteria in Solid Tumors (RECIST) represent the gold standard for response determination.¹ Although epithelial ovarian and peritoneal cancers are often assessed radiographically according to RECIST, clinical management is often guided by the less invasive and more cost-effective serum CA-125 level as a surrogate to RECIST. Gynecologic Cancer Intergroup (GCIG) CA-125 criteria have demonstrated a reasonable association with RECIST-defined response and progression in retrospective studies of patients treated with cytotoxic therapies.²⁻⁶ Therefore, over the last decade, CA-125 has been incorporated into the assessment of disease in some clinical trials examining cytotoxic agents. It is unclear whether newer biologic targeted therapies, such as anti-angiogenic agents, could have an impact on CA-125 levels independent of tumor burden. If so, the accuracy of CA-125 in disease assessment could be compromised. Incorrect assessment of disease status by surrogate measures such as CA-125 might lead to premature discontinuation of, or rejection of, active therapy.

Gynecologic Oncology Group (GOG) Protocol 170-D was a phase II evaluation of single-agent bevacizumab in patients with persistent or recurrent ovarian or peritoneal carcinoma with primary endpoints of progression-free survival (PFS) at 6 months and response as determined by RECIST.⁷ CA-125 measurements were collected, but these values were only required to confirm RECIST-defined complete responses.

The primary objective of this study was to assess the interactive and independent values of serum CA-125 and RECIST as measures of disease response or determinants of progression in the context of treatment with anti-angiogenic agent, bevacizumab, whose mechanism of action is unlike traditional cytotoxic agents. The secondary objective was to explore the prognostic significance of CA-125 and RECIST-defined responses and progressions.

PATIENTS AND METHODS

This is a retrospective analysis of serum CA-125 measurements recorded in patients enrolled on GOG Protocol 170-D. Details regarding the design and results of this study have been previously published⁷, but in summary, GOG 170-D was a multi-center phase II evaluation of single-agent bevacizumab at 15 mg/kg intravenously every 21 days in patients with histologically-confirmed recurrent or persistent ovarian or peritoneal carcinoma. The original study received local Institutional Review Board (IRB) approval. Patients with 1-2 prior regimens, of platinum-free interval $\leq$ 12 months with 1 prior platinum regimen or any interval with 2 such regimens, and measurable disease were eligible. The study's primary endpoints were the proportion of patients responding or who were progression-free (PFS) at 6 months as determined by RECIST.¹ CA-125 measurements were only required to confirm

a complete response in patients who had complete disappearance of disease on imaging. The final cohort consisted of 62 evaluable patients, 41 (66%) of whom had received 2 prior regimens and 26 (42%) of whom were considered platinum-resistant (platinum-free interval < 6 months). The overall response rate by RECIST for the entire cohort was 21% (2 complete and 11 partial responses), and 25 (40.3%) patients were PFS at 6 months. These results exceeded the thresholds of 10 responses and 13 patients with PFS at 6 months, supporting further investigation of bevacizumab in patients with epithelial ovarian and related cancers.

CA-125 levels were measured within 14 days before study entry and prior to each cycle of bevacizumab, and were not recorded after treatment was discontinued for either RECIST-defined disease progression or unacceptable toxicity. Details regarding the methodology of CA-125 measurement such as assay type and reference ranges were not available. Therefore, the upper limit of normal (ULN) was defined as a serum CA-125 concentration of 35 units/mL. Modified GCIG criteria were applied to CA-125 values to determine both progression and response. Specifically, progression was defined as a two-fold increase in the ULN if the nadir value was less than the ULN, a two-fold increase in the nadir value if the nadir value was greater than the ULN or death.^{3,4}

Response was defined as at least a 50% reduction in baseline CA-125 sustained over 28 days.^{5,6} Response by CA-125 was further refined in this report. Patients with CA-125 reduction below 35 units/mL, sustained for at least 28 days, were deemed to have a complete/full response. Otherwise, patients meeting the response criteria were classified as having partial responses. Patients who progressed by CA-125 within 8 weeks were categorized as having progressive disease and those who had at least 2 serum measurements (for at least 56 days after study entry), indicating none of the above categories were classified as having stable disease. Patients whose baseline CA-125 levels were less than twice the ULN prior to treatment were considered not evaluable by CA-125 criteria, and were excluded from response evaluations. Some evaluable patients did not submit enough data to determine a response classification, so they were classified as “Indeterminate for Response” and included in the calculation of the proportion responding (in the denominator as treatment failures).

Statistical methods

Time at risk for overall survival (OS) was assessed from study entry until death or date last seen. Time at risk for PFS was assessed from study entry until date of progression (by either RECIST or CA-125) or death (which ever occurred first), or date last seen. The estimate of PFS by CA-125 is potentially biased since collection of serum was stopped in patients who progressed by RECIST. The time at risk for the PFI by RECIST was determined by standard procedures and defined from study entry until the date of progression or date last seen. For all of these measures, the date of last follow up was used to determine a censored observation period in cases where the endpoint was not observed. In contrast, the time at risk for PFI by CA-125 was from study entry until progression by CA-125 or the date of last serum collection (for censored cases).

Time dependent covariate analyses were conducted with the hazard of disease progression (by RECIST) modeled though a Cox proportional hazards (PH) model as a function of the patients' state of disease progression (or response) by CA-125, using the method outlined by Buyse and Piedbois.⁸ At an event time, patients within the risk set were categorized as being in a state of progression if their CA-125 values were greater than twice the ULN or maximum of their nadir value. In a separate analysis, patients were likewise categorized to be in a state of response if their most recent CA-125 values were no greater than 50% of

their baseline levels. All 62 patients were included in the analysis of progression whereas only patients evaluable for response by CA-125 were included in the analysis of response.

A similar time dependent covariate analysis was done for the hazard of death. The covariates in these analyses were response as well as progression (by both RECIST and CA-125)^{9,10}. The 4 types of analyses were conducted separately. A patient's covariate was initially set to zero until the outcome of interest was met (e.g. response by CA-125). Then the variable was permanently set to the value 1. The analyses were conducted in this manner because many patients survive well beyond the timeframe of a clinical trial. In addition to univariate covariate analyses, multivariate analyses were conducted to assess the significance of these factors in the presence of potential confounders (performance status and platinum sensitivity).

A landmark analysis is often considered a survival analysis where the starting point for time at risk is reset from the time of study entry to a later time when most (or all patients) have observed the response of interest. Those patients who die before the start point are excluded from the analysis. Then OS can be examined by stratifying on response without issues involved in causal ordering.¹¹ A landmark analysis could not be conducted with RECIST tumor response since the time until tumor responses was unusually long with this treatment. This would require a significant proportion of patients to be excluded from the analysis. However, CA-125 responses were quickly observed, enabling an easy comparison of these groups through relatively standard techniques.

RESULTS

Sixty-two patients were eligible and evaluable on clinical protocol.⁷ Serum CA-125 levels over time were highly variable, and in several patients, CA-125 levels fluctuated in an oscillating pattern [Appendix A]. Determination of progression was limited by lack of CA-125 data following RECIST-defined progression, but progressions that were defined by death alone falsely prolonged PFS time. Therefore, a less-biased progression-free interval (PFI) was employed, defining progression by CA-125 only and censoring patients after their last CA-125 measurement. Kaplan-Meier (KM) estimates of PFS by RECIST and PFI by CA-125 were fairly comparable (Figure 1). The median PFS using RECIST criteria was 4.7 months, and the median PFI using CA-125 was 5.2 months. Likewise, the marginal distributions of PFS by RECIST and CA-125 were quite similar (KM curves not shown) with median estimates equal to 4.7 and 5.6 months, respectively. However, a scatter plot (Figure 2) of the times until the event for each individual shows the PFS and PFI measures are not redundant. If the 2 types of events were fully redundant, the points would fall on the line in the figure. On the contrary, this plot shows a considerable amount of scatter around the line. Of the 25 patients who were PFS at 6 months, 10 had already demonstrated CA-125-determined progression, which were confirmed by subsequent values in 9 cases. Perhaps more importantly, in 8 (12.9%) of the 62 cases, CA-125 progression preceded RECIST-defined progression from 5.7 to 38 months (Figure 2). CA-125 plots of these 8 patients are illustrated in Appendix A, with times to progression by CA-125 and RECIST separately denoted. Two general patterns of CA-125 trends were observed: one demonstrating an oscillating rise-and-fall pattern (cases 7, 13 and 33) and another showing a slow increase over time (cases 14, 15, 27, 49, and 57).

Thirty (48%) patients were evaluable for response by CA-125 with 32 exclusions due to baseline CA-125 < 35 or lack of follow-up data (Table 1). When dichotomizing patients by response versus not (excluding those not evaluable or indeterminate; a total of 29 patients), the odds ratio of responding was found to be 2.41 (95% C.I. 0.35 – 19.1; p=0.526). Utilizing the ordinal character of response, Kendall's tau-b, a measure of association-like correlation,

was found to be 0.19 ($p=0.30$).¹² The proportion responding as determined by CA-125 criteria was 14 out of 45 (31.1%). In comparison, the proportion responding by RECIST was 13 out of 62 (21.0%). Time to determine CA-125 response to bevacizumab was relatively short (median=0.90 months, minimum = 0.56 months, Figure 3A) compared to the time to response by RECIST (median=3.22 months, Figure 3B) and to OS (median=16.92 months, first quartile = 9.10 months). A landmark-adjusted Kaplan-Meier estimate of OS demonstrated a visually significant difference in distribution of OS between CA-125-defined responders (median OS 34.0 months) and CA-125-defined non-responders (median OS=11.8 months) as shown in Figure 4. A log-rank test for equivalency was statistically significant ($p=0.0037$, unadjusted for multiplicity) with an estimate of the proportional hazard ratio of 0.36 (95% CI 0.178 – 0.737), indicating that responders by CA-125 were more likely to survive longer than non-responders.

The results of time dependent covariate analyses of the hazard of progression by RECIST as a function of the patients' states of disease progression (or response) by CA-125 indicate a strong association between the patients' state of disease progression (or response) by CA-125 and the hazard of progression by RECIST. A patient in a state of disease progression by CA-125 has 5.2 (95% CI 2.7 – 9.7; $p<0.0001$) times the risk of progressing by RECIST than a patient who is not in a state of progression by CA-125. Additionally, a patient who is in a state of response by CA-125 has 19% (95% CI 6.9 – 55%; $p=0.002$) the risk of progression by RECIST than a patient who is not in a state of response.

Table 2 summarizes the results of the time dependent analyses of the hazard of death as a function of the patients' response (by RECIST or CA-125) and progression (also by RECIST or CA-125). The multivariate analyses included the prognostic variables platinum sensitivity and initial performance status, which did not vary as a function of time. Both response by CA-125 and RECIST were potent prognostic factors for OS. Also, progression as defined by RECIST was strongly associated with the hazard of death, but progression by CA-125 was not a significant prognostic factor in OS (HR = 1.1; 95% CI = 0.63-1.94) despite being associated with progression by RECIST.

DISCUSSION

Assessment of disease progression by CA-125 has been advocated by the GCIG, especially in phase II trials in recurrent disease, citing advantages that include earlier determination of treatment failure, increased frequency of endpoint events, cost-savings over imaging assessments, and inclusion of patients without measurable disease.³⁻⁶ This argument was presented to the U.S. Food and Drug Administration (FDA) in a public workshop addressing endpoints in ovarian cancer clinical trials of cytotoxic therapy, and the conclusion of the expert panel was that CA-125 was best utilized as part of a composite endpoint (with radiographic, clinical, and CA-125 components), and that assessment of both progression and response by CA-125 still requires prospective validation.¹³ In general, our data demonstrated patterns of CA125 change that varied among patients, and uncovered 8 (12.9%) patients who continued on therapy for at least 5.7 months after progression by CA-125 who did not experience progression by RECIST in that interval. This finding was observed in a previously-published report of 15 patients treated with bevacizumab in combination with sorafenib, where CA-125-defined progression preceded RECIST-defined progression in 3 patients.¹⁴ Our findings are hypothesis-generating and might have important implications for the design of future clinical trials and the management of patients on bevacizumab or other anti-angiogenic therapy.

In the GOG 170-D cohort, CA-125- and RECIST-determined median times to progression were similar, and the product-limit estimate of the proportion of patients 6 month PFS

differed only slightly according to CA-125 and RECIST at 40.9% and 41%, respectively. CA-125 progression “lead time” has been previously described in a retrospective analysis of patients randomized to cisplatin plus paclitaxel or cisplatin plus cyclophosphamide on GOG 111, where CA-125 progression preceded progression by RECIST in 254 of 456 patients by up to 650 days (median=95 days).² Despite a possible “lead time” effect in a small sample size, if progression had been assessed by CA-125 alone in 170-D (under the assumption of a similar distribution of PFS for a historical control), the threshold value required to satisfy the primary 6-month PFS endpoint (13 patients PFS at 6 months) would still have been achieved, deeming bevacizumab worthy of further investigation. However, bevacizumab therapy would have been discontinued in 8 (12.9%) patients from 5.7 to 38 months before RECIST-progression. It is possible that the tumors of these 8 patients, are biologically distinct from tumors in patients whose CA-125 progression time more closely correlates with RECIST or death. The best explanation for discordance is that the anti-angiogenic mechanism is inhibiting disease expansion, invasion, and metastases, but not able to control tumor cell proliferation as well. In some cases (those with the oscillating pattern), an anti-tumor proliferative effect may also be operative.

Of the 45 patients evaluable for response by CA-125, 14 (31%) responses were documented. Again, had the response endpoint been assessed by CA-125 alone, bevacizumab would have still been considered worthy of further investigation. CA-125-defined responses occurred within 2.3 months of study entry (before the third cycle of therapy) and, as a whole, preceded RECIST-defined responses.

An exploratory analysis of associations between CA-125- and RECIST-defined progression and response and OS was performed, and response by CA-125 was prognostic whereas progression by CA-125 was not. Specifically, RECIST-defined progression was associated with diminished OS that was statistically significant after controlling for platinum sensitivity and performance status. CA-125-defined progression did not have the same association with OS. This result sheds some doubt on the utility of CA-125 progression as a surrogate marker for OS since good prognostic value is a necessary condition for a good surrogate. We speculate that the association is not strong enough to carry a significant result into OS. That is to say that there could have been a sufficient number of discordant times to progression by CA-125 to render this variable insignificant when evaluating with hazard of death. Alternatively, the lack of an association could have resulted from censoring after progression by RECIST. On the other hand, the strong association between clinical progression and OS makes this variable a potential candidate for surrogacy but by no means validates it (i.e. a variable with good prognostic value is not a sufficient condition to make it a good surrogate; a simple example is initial performance status).

Consistent with previously published reports evaluating cytotoxic therapies,¹⁵⁻²⁶ CA-125-defined response was independently associated with improved OS. In this report, RECIST-defined response was also associated with statistically significant improvement in OS. This finding is somewhat provocative because GOG 170-D reported unexpected RECIST-defined responses to bevacizumab and previous publications have reported a lack of association between RECIST-defined response and survival in patients treated with cytotoxic therapies.^{17,20}

The lack of a statistically significant association between response by CA-125 and response by RECIST is probably the result of a small sample size (only 29 patients were evaluable for both endpoints). We suspect that a larger sample size would yield a statistically significant result. The relatively small level of association observed in this study (e.g. odds ratio = 2.4 and Kendall's tau-b = 0.19) was surprising. We suspect the low level of association was

caused mostly by discordant responses by CA-125 who were stable disease (8 cases) or progressive disease (1 case) by RECIST.

In summary, though GCIG CA-125 criteria would have generated the same conclusion as RECIST for response and 6 month PFS, approximately 10-15% would have discontinued therapy earlier had treatment decisions been based on CA-125 progression alone. This number is not insignificant since treatment options are limited for women with recurrent cancer, especially for those with platinum-resistant disease. Moreover, though GCIG-defined progression is recommended for use only as part of a composite index, GOG 0218, a phase III trial evaluating bevacizumab in the front-line setting, utilized GCIG progression as an independent measure of treatment failure. Inclusion of GCIG criteria alone to define progression might have been premature given the discrepancy identified in the current investigation, but GOG-218 will provide a unique opportunity to evaluate the prospective application of GCIG criteria.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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RESEARCH HIGHLIGHTS

- CA125-defined response and progression were assessed for women with recurrent ovarian cancer
- CA125-defined response and progression correlated with RECIST-defined response and progression in most cases, but CA125-defined progression preceded RECIST-defined progression, in a few cases by several months
- CA125-defined response to bevacizumab was associated with a statistically significant correlation with overall survival.

Figure 1.

Kaplan-Meier estimates of the progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria and modified Gynecologic Cancer InterGroup (GCIG) CA-125 criteria for available patients on GOG 170D. Median PFS by RECIST was 4.7 months and by CA-125 was 5.2 months.

Figure 2.

A scatter plot of individual outcomes for time to failure (TTF) in months by RECIST criteria (PFS endpoint) along the vertical scale and TTF in months by modified GCIG criteria for CA-125 (PFI endpoint, horizontal scale). Two groups become apparent in this presentation. Group 1, within the oval near the line, represents individuals who appear to show signs of progression by both criteria at roughly the same time. Group 2, within circles above the line, represents individuals with signs of progression by CA-125 sooner than by RECIST or death (false positives). Had patients continued to submit CA-125 data after clinical progression, it is possible that a third group could have revealed itself to the right of the line as those not having rising CA-125 in spite of clinical progression (false negatives).

Survival and Time to Response by CA125

Figure 3.

Kaplan-Meier (KM) estimate of the survival curve for patients who eventually experience a response with the KM estimate of overall survival (OS) as determined by CA125 (3A) and by RECIST (3B). Note that all CA125 responses were documented within 2.3 months of study entry, and that most patients experience a response by CA-125 before many patients in the sample die (3A), making a Landmark Analysis easier. Figure 3B shows that the time until response by RECIST is much more dispersed, making a Landmark Analysis more difficult to conduct.

Figure 4.

A Landmark Analysis of overall survival for patients who have a CA-125 response (dashed line) and not (solid line), where median survival was 34.0 versus 10.4 for responders and non-responders, respectively. Log-rank test for equivalency was statistically significant ($p=0.0037$, unadjusted for multiplicity) with an estimate of the Cox proportional hazard ratio of 0.36 (95% CI 0.178 – 0.737), indicating that responders by CA-125 were more likely to survive longer than non-responders and CA125 response might have significant prognostic value in addition to potential value as a surrogate variable.

Case Observed=27

Patient's Time of First Progression by CA-125 in Days After Entry Was: 105
 Patient's Progression-Free Survival in Days After Entry Was: 279

Case Observed=33

Patient's Time of First Progression by CA-125 in Days After Entry Was: 146
 Patient's Progression-Free Survival in Days After Entry Was: 392

Appendix A.

CA-125 patterns over time on study (day 0=date of entry) for patients whose CA-125-defined progression preceded RECIST-defined progression by at least 5.7 months. The first arrow denotes the time of CA-125-defined progression. All patients had RECIST-defined

progression by day 700 except for case 7 whose RECIST-defined progression occurred at Day 1327 (days 701-1327 not shown). Please note x-axis scale differences.

Table 1

Cross table of response by RECIST with response by CA125, with patients showing agreement between RECIST- and CA125-defined responses shown in bold.

Response By RECIST	Response by CA-125					
	CR	PR	SD	PD	DT	NE
CR	0	0	0	0	0	2
PR	3	3	0	0	0	11
		2				
SD	2	6		0	4	11
			9			
PD	0	1	1		9	3
				2		
DT	0	0	0	0		0
					1	
Total	5	9	13	2	14	19
						62

CR = Complete response, PR = Partial response, SD = Stable disease, PD = Progressive disease, DT = Indeterminate for response, NE = Not evaluable.

Table 2

Table of the hazard ratios of death for patients who experienced (as time dependent covariates) either RECIST response, RECIST progression, response by CA-125, and progression by CA-125 versus those who did not. Hazard ratios are presented for both univariate analyses and adjusted multivariate analyses.

Univariate Analyses	HR	95% C.I. for HR
RECIST Response	0.41	0.200 – 0.852
RECIST Progression	13.84	4.055 – 47.227
CA-125 Response	0.33	0.162 – 0.684
CA-125 Progression	1.16	0.665 – 2.046
Multivariable Analyses*		
Clinical Response	0.41	0.190 – 0.871
Clinical Progression	13.90	4.204 – 45.968
CA-125 Response	0.27	0.117 – 0.599
CA-125 Progression	1.00	0.547 – 1.933

The multivariable analyses included the known prognostic factors platinum sensitivity and performance status. HR = Hazard ratio, C.I. = Confidence interval.

Table 3

Table of hazard ratios for RECIST progression for patients who are in a state of progression by CA-125 or in a state of response by CA-125

Analysis	HR *	95% C.I. for HR *	p-value
Progression	5.434	2.899 – 10.19	<0.0001
Response	0.191	0.067 – 0.546	0.0020

* HR = Hazard ratio, C.I. = Confidence interval.