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A Gynecologic Oncology Group Study of serum CA-125 levels in patients with stage III optimally debulked ovarian cancer treated with intraperitoneal compared to intravenous chemotherapy: An analysis of patients enrolled in GOG 172

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Abstract

Objective—Serum CA-125 values have been advocated in the monitoring of ovarian cancer patients receiving intravenous (IV) chemotherapy. This evaluation sought to determine if the CA-125 test can be used to monitor treatment effect among patients receiving intraperitoneal chemotherapy (IP).

Methods—Patient charts from a phase III clinical trial (GOG 172) were retrospectively reviewed. Serum CA-125 levels prior to each cycle of therapy were collected and compared between the IV and IP chemotherapy delivery. The association between CA-125 and progression-free survival (PFS) or overall survival (OS) was estimated and the homogeneity of the results between IP and IV chemotherapy was assessed.

Results—A total of 177 patients were treated with IV chemotherapy and 165 patients with IP chemotherapy with CA-125 data available were included in this analysis. The observed difference was not statistically significant in median CA-125 levels between the IV and IP arms at any time point ($P > 0.05$ for all). Following surgery and adjuvant chemotherapy, patients with an abnormal CA-125 > 35 U/ml were 2.45 times more likely to have disease progression (95% CI: 1.52–3.95, $P < 0.001$) and 2.78 times more likely to die of disease (95% CI: 1.66–4.65, $P < 0.001$), compared to those with a CA-125 < 35 U/ml. These results were consistent with IP and IV chemotherapy.

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Conflict of interest statement

The authors have no conflict of interest to disclose.

Conclusion—Serum CA-125 levels decrease in a similar manner during IP chemotherapy when compared to IV chemotherapy. Serum CA-125 algorithms for monitoring treatment effect that have been established for IV chemotherapy may also be applied for patients receiving IP chemotherapy.

Keywords

CA-125; Intraperitoneal chemotherapy; Ovarian cancer

Introduction

Ovarian cancer will affect approximately 21,650 patients in the United States resulting in 15,520 deaths in 2008 [1]. Approximately 80% of the patients will present with Stages III to IV cancer. Traditionally surgical cytoreduction followed by platinum based chemotherapy has been the cornerstone of treatment of this population. Early normalization of the CA-125 during adjuvant postoperative chemotherapy among patients with advanced stage ovarian cancer is associated with improved survival [2–4]. Monitoring serum CA-125 levels during therapy is a predictor of survival and may allow for early identification of patients who are not responding to therapy and require a change in treatment.

Recent studies have suggested survival advantages associated with intraperitoneal (IP) infusion of chemotherapy which allows for high doses of chemotherapy to be infused because of the slow and incomplete transit of intraperitoneal agents into the circulation [5–7]. The use of IP chemotherapy, with cisplatin and paclitaxel, may cause irritation of the peritoneal cavity and theoretically increase CA-125 levels. Makhija et al. previously reported on serum CA-125 levels in patients who have undergone surgery and were then treated with intraperitoneal ³²P. Their results found patients treated with intraperitoneal ³²P had elevated serum CA-125 levels, and that this tumor marker may not accurately reflect recurrent or progressive ovarian cancer [8]. Richardson et al. in a single institution review did not demonstrate any difference in the rate of decline of CA-125 levels when comparing patients treated with intravenous (IV) to IP chemotherapy for advanced ovarian cancer [9]. The present analysis was performed utilizing data from a large cooperative group clinical trial to evaluate the utility of CA-125 levels in patients treated with IP versus IV chemotherapy.

Methods

Patient charts from a phase III clinical trial, Gynecologic Oncology Group (GOG) study 172, were retrospectively reviewed. GOG-172 was a phase III randomized trial of IV versus IP cisplatin/paclitaxel in patients with optimally-resected, stage III epithelial ovarian cancer (EOC) or primary peritoneal carcinoma. Details regarding eligibility criteria, treatment and clinical outcomes have been previously published [5]. Serum CA-125 levels prior to each cycle of therapy were collected and compared between the IV and IP groups. The analysis was conducted according to the treatment that the patients actually received. Patients who were randomized to a treatment arm, but did not receive the chemotherapy as prescribed were excluded from the analysis at that assessment point. Therefore, to be included in this

analysis patients must have CA-125 data available and have received the prescribed protocol therapy at each cycle. The comparisons included the rate of normalization (defined as ≤ 35 U/ml) and the median CA-125 level at each assessment point. All patients had signed written informed consent and all participating institutions received local institutional review board approval for the study.

The prognostic value of CA-125 measured at pre-treatment, pre-second cycle; pre-fourth cycle and pre-sixth cycle was assessed. The relative risks of disease progression and death for >35 versus ≤ 35 U/ml were estimated from a Cox model adjusted for tumor residual, histology and type of chemotherapy (IV or IP). The interaction between type of treatment and CA-125 was evaluated to determine if the results were consistent between IP and IV patients. In addition, the association of CA-125 with clinical outcome was also assessed by treating CA-125 as a continuous variable, where the raw CA-125 level was transformed to a logarithmic scale [$\text{Log}_2(\text{CA-125})$]. The relative risk was interpreted for one-unit increase in $\text{Log}_2(\text{CA-125})$, or one-fold increase in raw CA-125 level. Progression-free survival (PFS) and overall survival (OS) were also estimated using Kaplan–Meier procedure based on the level of CA-125 at end of chemotherapy (>35 versus ≤ 35 U/ml) for both IP and IV patients [9]. Cox proportional hazards model was used to determine hazard ratios for prognostic factors such as tumor residual, histology, and delivery of chemotherapy [10].

Results

Two hundred and ten (210) eligible patients were randomized to IV chemotherapy and 205 patients to IP chemotherapy. Two patients from the IV group and 16 patients from IP group who received no chemotherapy were excluded from this analysis. The demographic data of the patient populations for each subgroup has been previously described in the publication of GOG 172 and there were no differences with respect to age, stage, tumor grade, residual disease, and performance status between the IP and IV groups [5]. The number of patients with or without CA-125 data for each cycle is presented in Table 1. There was no statistical difference in the percentage of missing of CA-125 data. Missing data for each cycle of chemotherapy varied from 15–25% for IV chemotherapy and 8–24% for IP chemotherapy. The clinical characteristics were the same between patients with CA-125 data and those with missing data. The CA-125 level and the time to normalization by the type of treatment are shown in Fig. 1 and Table 2. Median CA-125 levels for patients treated with IP chemotherapy at pre-treatment cycle 1, pre-2nd, 3rd, 4th, 5th, and 6th cycles were 144, 39, 26, 16, 14, and 13 U/ml respectively, whereas median CA-125 levels for patients treated with IV chemotherapy were 149, 40, 22, 16, 13, and 13 U/ml at pre-treatment, pre-2nd, 3rd, 4th, 5th, and 6th cycles respectively. The observed difference was not statistically significant between the IV and IP arms at any time point ($P>0.05$ for all). The CA-125 level experienced rapid reduction following the 1st cycle and became stable after the 3rd cycle of chemotherapy. Abnormal CA-125 (defined as a level >35 U/ml) was observed in 89% of patients at pre-treatment, 55% after one cycle, 21% after three cycles and 11% at the end of chemotherapy, with no difference between IV and IP groups ($P>0.05$).

We evaluated the prognostic value of CA-125 at pre-chemotherapy, pre-2nd, pre-4th, and pre-6th cycles. The relative risk of disease progression and death for >35 versus ≤ 35 U/ml

were estimated adjusted for tumor residual, histology and type of chemotherapy. There was no interaction between the type of treatment and CA125 (test for interaction: $P>0.05$ for all), suggesting the results were consistent between IV and IP groups. Thus, the hazard ratio was estimated as combining both IV and IP patients together. As shown in Table 3, the CA-125 level following treatment was significantly associated with outcome. After six cycles of chemotherapy, the risk of disease progression among patients with CA-125 >35 U/ml was 2.45 times (95% CI: 1.52–3.95, $P<0.001$) more than those with CA-125 level <35 U/ml and the risk of death was more than 2.78 times (95% CI: 1.66–4.65, $P<0.001$). Based on a continuous variable, a one-fold increase in CA-125 level led to a 35% increase in the risk of disease progression or 61% increase in the risk of death.

Figs. 2A and B demonstrate the PFS and OS of normal compared to abnormal CA-125 level at end of treatment, stratified by the type of treatment. Among patients with IV chemotherapy, the median PFS was 26.4 and 9.4 months, respectively, for normal and abnormal CA-125 ($P=0.005$); for patients treated with IP chemotherapy the median PFS was 30.5 and 16.8 months, respectively ($P=0.029$). Median OS for patients treated with intravenous chemotherapy and a normal CA-125 was 58.2 months, and for an abnormal CA-125 median OS was 20.7 months ($P=0.0003$); patients treated with IP chemotherapy had a median OS of 96.2 months for a normal CA-125 compared to 49.7 months for an abnormal CA-125 ($P=0.058$). Although patients on IP chemotherapy had improved PFS and OS in all subgroups compared to IV chemotherapy, the rates of normalization of CA-125 appeared similar between IV and IP patients.

Discussion

Bast et al. first described the CA-125 antigen as a proposed serum marker for patients with ovarian cancer and this is now commonly used to monitor response to therapy and detection of recurrent ovarian cancer [11,12]. The serum CA-125 levels are elevated in greater than 90% of patients with advanced stage epithelial ovarian cancer [13]. Markedly elevated CA-125 levels (>500 U/ml) have been associated with a low likelihood of achieving optimal cytoreduction, suggesting that elevations of this ovarian cancer biomarker are associated with tumor aggressiveness [2,3,14–18]. Zorn et al. performed a large analysis of several randomized trials in patients with advanced stage ovarian cancer and demonstrated that patients with a higher preoperative CA-125 had decreased survival [14]. Evaluating patients with normal CA-125, Peace et al. showed patients with a nadir value of <10 units/ml had a significantly improved survival when compared to patients having higher levels [16]. Additional reports evaluating the effect of nadir serum CA-125 values of patients and outcomes have been described [17,18]. Patients with low normal values had improved PFS when compared to patients with higher normal values [17,18].

The peritoneum is a tissue that has been reported to have a greater expression of CA-125 when compared to ovarian epithelium [19,20]. Zeimet et al. compared the CA-125 shedding of human peritoneal mesothelial cells to ovarian cancer cell lines. The authors demonstrated that mesothelial cells have a five-fold higher shedding of CA-125 when compared to ovarian cancer cell lines [19]. Patients with non malignant conditions of the peritoneum such as pelvic inflammatory disease, endometriosis, ruptured ectopic pregnancy, chronic renal

failure receiving intraperitoneal dialysis, liver cirrhosis may also demonstrate an increased CA-125 due to peritoneal inflammation [20–24]. Studies evaluating serum CA-125 levels after surgery have also demonstrated transient elevations of serum CA-125 levels that are not reflective of disease status [20,21]. Makhija et al. reported on patients with ovarian cancer treated surgery followed by adjuvant intraperitoneal ^{32}P [8]. These patients showed an elevated CA-125 level lasting for 6–12 months which was not reflective of recurrent disease. The results of our current study did not demonstrate any differences in serum CA-125 levels during treatment between the IV and IP groups.

The use of the CA-125 value is important in assessing primary response to therapy in patients with advanced ovarian cancer. Detection of patients who are not responding to adjuvant or salvage chemotherapy will allow for identification of patients who require alternative chemotherapy and may potentially decrease unnecessary side effects from ineffective treatments. Previous studies have reported on the use of CA-125 regression during primary therapy to predict response and survival in patients with advanced stage ovarian cancer [2–4]. Buller et al. reported that the rate of CA-125 regression and normalization is an important prognostic factor in patients with advanced ovarian cancer [25]. Richardson et al. showed no difference in CA-125 values in patients treated with IV compared to IP therapy [9]. Our current study agree with the Richardson study and showed that there was no difference in time to normalization of CA-125 values when comparing IV to IP treatment. We also evaluated PFS and OS comparing patients with normal serum CA-125 (<35 U/ml) to abnormal serum CA-125 levels (>35 U/ml) at pre-treatment, pre-2nd, pre-4th, and pre-6th cycles of chemotherapy and our results showed patients who had a normal CA-125 had an improved PFS and OS. The Kaplan–Meier survival curves demonstrated that at pre-sixth cycle of therapy, patients with a normal CA-125 had an improved survival in both the IP and IV treated patients. Patients with an abnormal CA-125 had decreased survival regardless of the delivery method for the chemotherapy.

This study is a retrospective review of CA125 levels in patients treated with IP chemotherapy and compared these levels to patients treated with IV chemotherapy and there are numerous limitations. These would include that the trial was not designed to specifically address this variable of CA-125 and time to normalization. The CA-125 data were missing in 16%–29% each cycle and the number of patients receiving IP chemotherapy. There is no reference laboratory and the CA-125 levels were assessed at local institutions and may differ in reference ranges. These data may only reflect the interaction with intraperitoneal cisplatin/paclitaxel and serum CA-125 levels. Richard et al. reported decreasing CA125 levels after removal of the intraperitoneal catheters, therefore suggesting an additional interaction between CA-125 levels and the intraperitoneal catheter device may exist [26]. In our current study the CA-125 levels in the intraperitoneal chemotherapy treated group were assessed with the IP catheter in place and data for CA-125 after catheter removal were not available.

This is the largest study to date describing CA-125 levels and trends in patients treated with IP cisplatin and paclitaxel. These results suggest that the same algorithms developed for patients treated with IV chemotherapy may be applied to patients who are being treated with IP chemotherapy. The theoretical increase in intraperitoneal irritation and increase in serum

CA-125 levels in patients treated with intraperitoneal chemotherapy is plausible however the results of this current study demonstrate that there is no difference in CA-125 levels. This retrospective review demonstrated that there was no difference in serum CA-125 levels irrespective of the delivery method of the chemotherapy (IP versus IV).

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Fig. 1.
CA-125 changes following intravenous (IV) and intraperitoneal (IP) chemotherapy.

Fig. 2.

(A) Kaplan–Meier estimate of progression-free survival based on normalization of CA-125 at end of chemotherapy for IV versus IP treatment. (B) Kaplan–Meier estimate of overall survival based on normalization of CA-125 at end of chemotherapy for IV versus IP treatment.

Table 1
Number of patients with CA-125 data for intravenous and intraperitoneal chemotherapy.

Cycle	Intravenous chemotherapy			Intraperitoneal chemotherapy		
	Expected	Observed	Missing (%)	Expected	Observed	Missing (%)
Pre-1st	208	177	31 (15)	189	165	24 (13)
Pre-2nd	200	149	51 (26)	149	122	27 (18)
Pre-3rd	191	150	41 (22)	119	91	28 (24)
Pre-4th	180	138	42 (23)	104	88	16 (15)
Pre-5th	178	144	34 (19)	97	80	17 (18)
Pre-6th	173	129	44 (25)	86	79	7 (8)

Table 2

CA-125 levels during treatment for intravenous versus intraperitoneal chemotherapy.

	Intravenous chemotherapy	Intraperitoneal chemotherapy
Baseline (pre-1st cycle)		
No. patients	177	165
35 U/ml, No. (%)	160 (90.4%)	146 (88.5%)
Median (25th–75th Pct)	149 (73–309)	144 (60–364)
Pre-2nd cycle		
No. patients	149	122
35 U/ml (%)	82 (55.0%)	67 (54.9%)
Median (25th–75th Pct)	40 (20–100)	39 (20–88)
Pre-3rd cycle		
No. patients	150	91
35 U/ml (%)	54 (36.0%)	31 (34.1%)
Median (25th–75th Pct)	22 (11–54)	26 (15–50)
Pre-4th cycle		
No. patients	138	88
35 U/ml (%)	31 (22.5%)	17 (19.3%)
Median (25th–75th Pct)	16 (9–30)	16 (10–28)
Pre-5th cycle		
No. patients	144	80
35 U/ml (%)	20 (13.9%)	11 (13.8%)
Median (25th–75th Pct)	13 (9–21)	14 (8–21)
Pre-6th cycle		
No. patients	129	79
35 U/ml (%)	13 (10.1%)	9 (11.4%)
Median (25th–75th Pct)	13 (8–19)	13 (8–19)

Data missing due to corresponding treatment not given or CA125 not reported by the institutes. No significant difference in CA125 between two treatments identified at any time point ($P>0.05$ for all).

Table 3

Association of CA-125 levels during treatment with progress-free survival (PFS) and overall survival (OS).

	PFS			OS		
	HR	95% C.I.	P value	HR	95% C.I.	P value
Baseline CA125						
Log ₂ (CA125)	1.10	1.02–1.18	0.009	1.09	1.01–1.17	0.032
35 versus < 35 U/ml	0.99	0.65–1.52	0.961	1.16	0.71–1.90	0.565
Pre-2nd cycle						
Log ₂ (CA125)	1.24	1.15–1.34	<0.001	1.26	1.16–1.37	<0.001
35 versus < 35 U/ml	1.98	1.47–2.66	<0.001	2.88	2.01–4.16	<0.001
Pre-4th cycle						
Log ₂ (CA125)	1.39	1.21–1.59	<0.001	1.46	1.26–1.68	<0.001
35 versus < 35 U/ml	1.80	1.27–2.56	0.001	1.94	1.31–2.85	<0.001
Pre-6th cycle						
Log ₂ (CA125)	1.35	1.13–1.61	0.001	1.61	1.32–1.96	<0.001
35 versus < 35 U/ml	2.45	1.52–3.95	<0.003	2.78	1.66–4.65	<0.001

Hazard ratio (HR) estimated from Cox model adjusted for tumor residual, histology and type of chemotherapy.