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Hormonal therapy for recurrent low-grade serous carcinoma of the ovary or peritoneum

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Abstract

Objective—To determine whether hormonal therapies have efficacy in patients with recurrent low-grade serous carcinoma of the ovary or peritoneum.

Methods—We searched departmental databases for patients with histologically-confirmed, evaluable, recurrent low-grade serous ovarian or peritoneal carcinoma who received hormonal therapy at our institution between 1989 and 2009. We retrospectively reviewed patients' medical records for demographic, disease, hormonal therapy, and estrogen receptor and progesterone receptor expression data. We used the Response Evaluation Criteria in Solid Tumors version 1.1 to determine patients' responses to hormonal therapy. Because patients could have received more than one evaluable hormonal therapy regimen, we chose to define the outcome metric as “patient-regimens.” Median time to disease progression (TTP) and overall survival (OS) were also calculated. Regression analysis was also performed.

Results—We identified 64 patients with recurrent low-grade serous carcinoma of the ovary or peritoneum. Patients' median TTP and median OS were 7.4 and 78.2 months, respectively. Patients received 89 separate hormonal patient-regimens, which produced an overall response rate of 9% (6 complete responses and 2 partial responses). Sixty-one percent of the patient-regimens resulted in a 6-month progression-free survival duration of at least 6 months. Patient-regimens

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involving ER+/PR+ disease produced a longer median TTP (8.9 months) than patient-regimens involving ER+/PR- disease did (6.2 months; $p = 0.053$). This difference approached but did not reach statistical significance.

Conclusions—Hormonal therapies have moderate anti-tumor activity in patients with recurrent low-grade serous carcinoma of the ovary or peritoneum. Further study to determine whether ER/PR expression status is a predictive biomarker for this rare cancer subtype is warranted.

Keywords

low-grade serous carcinoma; ovary; hormonal therapy

Introduction

Low-grade serous carcinoma, a distinct histotype of epithelial cancer of the ovary or peritoneum, has a unique morphology, molecular biology, and clinical behavior [1-10]. Low-grade serous carcinoma can arise *de novo* or from serous tumors of low malignant potential [9,11]. Studies have shown that low-grade serous carcinoma is less sensitive to conventional chemotherapy in the neoadjuvant, adjuvant, or recurrent settings than high-grade ovarian cancers, which are more common [9,12,13]. However, low-grade serous carcinoma is generally more indolent and is associated with much more favorable clinical outcomes than high-grade cancers [9].

Hormonal therapy, which plays an important role in the treatment of breast cancer [14-16], may also provide clinical benefit in some women with recurrent epithelial cancers of the ovary or peritoneum [17-22]. However, most studies of hormonal therapy for these cancers have included several subtypes of ovarian cancer, which limits one's ability to determine whether this clinical benefit is associated with a specific histological type or grade.

For several decades, we have used hormonal agents to treat patients with ovarian or peritoneal cancer [22-24]. Based on this experience, we came to believe that well-differentiated recurrent tumors tend to respond better to hormonal therapy than poorly differentiated recurrent tumors; consequently, we have used a variety of hormonal agents to treat women with recurrent low-grade serous carcinoma of the ovary or peritoneum. To determine whether hormonal therapy actually offers a benefit in patients with recurrent low-grade serous carcinoma of the ovary or peritoneum, we retrospectively analyzed information from patients with these tumor subtypes who underwent hormonal therapy at our center.

Material and methods

Patients

This study was approved by The University of Texas MD Anderson Cancer Center Institutional Review Board. We searched databases in MD Anderson's Department of Gynecologic Oncology to identify patients with histologically confirmed, evaluable recurrent low-grade serous carcinoma of the ovary or peritoneum who received hormonal therapy at MD Anderson between 1989 and 2009. Patients who had an original diagnosis of a serous tumor of low malignant potential and who then developed low-grade serous

carcinoma were also included in this study. We retrospectively reviewed those patients' medical records for demographic data, including age at diagnosis and race; and disease information, including date of diagnosis; disease stage based on International Federation of Gynecology and Obstetrics criteria; platinum sensitivity status; estrogen receptor (ER)/ progesterone receptor (PR) expression status; method(s) used to detect disease progression; and the date disease progression was detected. We recorded the number and type of systemic therapy regimens (hormonal or chemotherapy) patients received, start and completion dates of therapy, and clinical response to hormonal therapy. We also recorded patients' serum CA 125 levels at hormonal therapy initiation and completion and at the time of disease progression, imaging findings before and after hormonal therapy, and physical examination information, as well as the date of and patient status at last follow-up. Patients who received hormonal therapy in combination with chemotherapy were excluded.

Only those patients with sufficient clinical information enabling the evaluation of clinical response to hormonal therapy were included. Sufficient clinical information was defined as pre- and post-hormonal therapy radiographic imaging studies (computed tomography or positron emission tomography-computed tomography) indicating response, stable disease, or disease progression.

Pathology

Gynecologic pathologists (M.T.D. or A.M.) used MD Anderson's 2-tier system [1] to histologically confirm diagnoses of low-grade serous carcinoma of the ovary or peritoneum. Pathology review included examination of all cases.

Response criteria

The primary endpoint in the present study was response to hormonal therapy. Clinical response to hormonal therapy was assigned using the modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and/or the Gynecologic Cancer Intergroup serum CA 125 criteria [25,26]. Because of the retrospective nature of this study, we were unable to confirm patients' responses by a second imaging study. We considered patients to have stable disease if their disease measurements on follow-up met the criteria for stable disease at least once after the start of a particular hormonal therapy regimen for a minimum of 8 weeks. All responses based on RECIST 1.1 were determined by a single radiologist (R.B. I.).

Because patients could have received more than 1 hormonal therapy regimen, we defined the outcome metric as “patient-regimens,” a metric that we have used previously [13]. For example, one patient may have received multiple hormonal regimens at different times; by using patient-regimens as the outcome metric, we were able to include each distinct regimen in the analyses.

Immunohistochemical analysis

Tissue specimens were available for 50 of the 64 patients in the study and were tested for ER/PR; 27 were specimens of primary tumor and 23 were specimens of recurrent tumor. Immunohistochemical analysis for ER/PR expression status was performed on paraffin-

embedded sections of low-grade serous tumor, when available, using a Bond-Max automated immunostainer with a polymer detection system (Leica Microsystems, Buffalo Grove, IL). Briefly, tissue sections were deparaffinized using Bond Dewax solution, rinsed with series of alcohol solutions of decreasing alcohol concentration, and subjected to pretreatment with citrate buffer for 30 minutes for ER assessment or 20 minutes for PR assessment. The tissue sections were then exposed to 3.0% hydrogen peroxide to block endogenous peroxidase activity and incubated with a 1:35 dilution of an anti-ER antibody (clone 6F11, Novocastra, Buffalo Grove, IL) or a 1:200 dilution of an anti-PR antibody (clone PgR1294, DAKO, Carpinteria, CA). 3,3′-Diaminobenzidine (DAB) was used as the chromogen to visualize the immunoreaction and hematoxylin was used as the counterstain. We defined receptor positivity as nuclear staining of ≥1%.

Statistical analysis

Statistical analyses were performed using SPSS 17.0 software (SPSS, Cook County, Chicago, IL). Time to progression (TTP) was calculated from the initiation of a hormonal regimen until the date of disease progression or recurrence. Overall survival duration was calculated from the date of diagnosis to the date of last contact or death of the patient. For those patients whose original diagnosis was a serous tumor of low malignant potential and then recurred with low-grade serous carcinoma, the date of diagnosis was defined as the date of the initial recurrence with low-grade serous carcinoma. Median overall survival duration was estimated using the method of Kaplan and Meier [27]. Summary statistics were used to describe the study population. Chisquare and Fisher's exact tests were used to evaluate associations between categorical variables. Cox proportional hazards regression, the log-rank test, and the Kaplan-Meier method were used to assess survival outcomes. Multivariate regression analyses included covariates with P values ≤ .30 from univariate analyses. All tests were 2-sided, *P* values of <0.05 were considered statistically significant.

Results

We identified 133 patients with recurrent low-grade serous carcinoma of the ovary or peritoneum who received a total of 219 separate hormonal therapy regimens (“patient-regimens”) at MD Anderson. Of these 133 patients, 64 patients for whom sufficient clinical information was available to determine response met the inclusion criteria of the study. These 64 patients received 89 hormonal therapy regimens (patient-regimens). Forty-eight patients received 1 hormonal therapy regimen, 11 patients received 2 regimens, two each received 3 and 4 regimens, and one patient received 5 regimens.

The 64 patients' demographic data and disease characteristics at initial diagnosis are summarized in Table 1. The response data by order of regimen administration, including both chemotherapy and hormonal therapy, are summarized in Table 2.

Patients' responses to hormonal therapy by agent and by platinum sensitivity status are presented in Table 3. All objective responses were observed within the first 4 regimens of systemic treatment.

Of the 89 patient-regimens, 6 (6.7%) produced a complete response, and 2 (2.2%) produced a partial response (overall response rate, 9%). Of the 52 patient-regimens that involved platinum-sensitive disease, 5 produced a complete response (1 to anastrozole, 3 to letrozole, and 1 to tamoxifen), and 2 produced partial responses to letrozole (overall response rate, 13.5%). Of the 37 patient-regimens involving platinum-resistant disease, 1 produced a complete response to letrozole (overall response rate, 2.7%). Response by order of regimen administration was 14% for regimen #2 (first regimen for relapse), 12% for regimen #3, and 14% for regimen #4.

The same trend held for patient-regimens resulting in stable disease: of the 55 patient-regimens that resulted in stable disease, 36 (65.5%) involved platinum-sensitive disease, and 19 (34.5%) involved platinum-resistant disease ($p = 0.02$). The proportion of patient-regimens involving platinum-sensitive disease that resulted in a complete response, a partial response, or stable disease (82.7%), was significantly higher than the proportion of patient-regimens involving platinum-resistant disease that resulted in a complete response, a partial response, or stable disease (54.1%; $p = 0.003$). Details of the 8 patient-regimens that produced an objective response are summarized in Table 4.

Pre- and post-treatment serum CA 125 values were available for all 89 patient-regimens (Table 5). Of the 8 patient-regimens that produced an objective response, 4 (50%) were associated with a decrease in serum CA 125 levels of > 50%.

The median TTP of the 89 patient-regimens was 7.4 months (95% confidence interval [CI], 6.0-8.9). The median TTP of the 52 patient-regimens that involved platinum-sensitive disease (8.9 months; 95% CI, 4.7-13.2) was significantly longer than that of the 37 patient-regimens involving platinum-resistant disease (5.73 months; 95% CI, 4.3-7.2; $p = 0.003$ by the log rank test). The median TTP of the patient-regimens involving ER+/PR+ disease (8.9 months; 95% CI, 3.24-14.6]) was longer than that of the patient-regimens involving ER +/PR- disease (6.2 months; 95% CI, 5.59-6.55; $p = 0.053$) using the log-rank test.

Sixty-one percent of the patient-regimens elicited a progression-free survival duration of ≥6 months. The 6-month progression-free survival rate was significantly higher among patient-regimens involving platinum-sensitive disease (73%) than among patient-regimens involving platinum-resistant disease (46%; $p = 0.007$). The 64 patients' median overall survival duration from initial diagnosis was 78.2 months (95% CI, 44.2-112.2).

ER/PR expression data were available for 50 patients; the results of the univariate analysis of these patients are summarized in Table 6. Age at first hormonal treatment was significantly associated with the likelihood of disease progression ($p<0.001$). Patients 40-65 years old had a longer median TTP (hazard ratio [HR] = 0.43) than patients younger than 40 years ($p = 0.02$) or older than 65 years ($p = 0.017$). In addition, patients with ER+/PR- tumors had a shorter median TTP (HR = 1.8; 95% CI, 0.98-3.30) than patients with ER+/PR + tumors did; this observation approached but did not reach statistical significance ($p = 0.056$).

Variables for which the univariate analysis yielded p-values ≤ 0.3--disease site, platinum sensitivity status, ER/PR status, pre-hormonal therapy serum CA 125 value, and age at time

of hormonal therapy--were included in the multivariate analysis. ER+/PR- disease was associated with a shorter TTP (HR, 1.96; 95% CI, 1.06-3.61; $p = 0.03$). Patients 40-65 years old had a longer median TTP than patients <40 years old (HR, .39; 95% CI, 0.19-0.82; $p = 0.013$) and patients >65 years old (HR, 2.97; 95% CI, 1.19-7.43; $p = 0.02$).

For the 89 patient-regimens, the univariate analyses revealed that higher regimen order, pre-hormonal therapy serum CA 125 levels >35 U/mL, changes in serum CA 125 levels from the beginning to the end of hormonal treatment that did not involve a decrease of >50%, and age ≤ 40 years or ≥65 years and older at the time of hormonal treatment were associated with shorter TTP. Multivariate analysis revealed that pre-hormonal serum CA 125 levels > 35 U/mL were associated with a shorter TTP (HR, 2.15; 95% CI, 1.19-3.88; $p = 0.01$).

Discussion

Based on the present study's findings, we conclude that hormonal therapy is moderately active against low-grade serous carcinoma of the ovary or peritoneum. The overall response and stable disease rates of the 89 patient-regimens we analyzed were 9% and 62%, respectively. Thus, over 70% of patients experienced a clinical benefit. In addition, response was more likely associated with platinum-sensitivity status and a decrease in serum CA 125 levels of >50% during treatment. Longer TTP was associated with platinum-sensitive disease, ER+/PR+ disease, and age 40-65 years. When all 89 patient-regimens were analyzed in a regression model, pre-hormonal therapy, CA 125 level of > 35 U/mL, and any trend other than a > 50% decrease in CA 125 level during therapy were associated with significantly shorter TTP.

Although we and others have long suspected that hormonal therapy is effective in some patients with low-grade serous carcinoma--possibly even more so than in women with other epithelial ovarian cancer subtypes--ours is the first study that firmly establishes hormonal therapy as a component in the treatment of this subtype.

Many researchers have investigated hormonal therapy for ovarian cancer. However, essentially all of these studies included all ovarian cancer subtypes and histologic grades, rendering the interpretation of the efficacy of hormonal therapy for specific subtypes infeasible [17-24, 28-34].

Tamoxifen has demonstrated modest activity in ovarian cancer [17, 18, 23, 28-30]. Williams et al. reviewed 14 studies of tamoxifen for ovarian cancer and reported an overall objective response rate of 10% (range, 0-56%) and a stable disease rate of 32% (range, 0-83%) [17]. Marth et al. found that patients with endometrioid tumors who were treated with tamoxifen had a significantly higher remission rate than did patients with other cell types; that tamoxifen did not elicit a response in patients with clear cell carcinomas; and that grade 1 tumors were not associated with a higher rate of response to tamoxifen [18].

The use of aromatase inhibitors in all subtypes of ovarian cancer has also been investigated [20-22, 31, 32]. del Carmen et al. found that of 29 women with recurrent or persistent, measurable ovarian, peritoneal, or fallopian tube cancers, only 1 (3%) had a partial response to anastrozole [20]. Papadimitriou et al. found 1 complete response and 2 partial responses

(overall response rate, 15%) in 21 patients with measurable recurrent ovarian cancer [31]. In another phase II trial of letrozole, Smyth et al. reported a response rate of 17% and a 6-month progression-free survival rate of 26% in 42 patients with recurrent ER+ ovarian cancer who were evaluable for serum CA 125 response; of the 33 patients who had measurable disease, 3 patients (9%) had a partial response [21].

Several researchers have also investigated gonadotropin-releasing analogues for the treatment of recurrent ovarian cancer [19,33,34]. Kavanagh et al. observed 4 (17%) partial responses to leuprolide acetate in 18 patients with recurrent ovarian cancer, 2 of whom had grade 1 serous carcinoma [33]. Paskeviciute et al. noted 1 complete response and 2 partial responses (overall response rate, 9%) in 32 patients with recurrent ovarian cancer [19].

In a previous study detailing our experience with conventional chemotherapy in women with recurrent low-grade serous carcinoma, we found a response rate of less than 5%. However, the median TTP (7.2 months) and stable disease rate (60.2%) were quite similar to those in the present study (7.4 months and 62%, respectively) [13].

Another important issue for consideration is whether hormone receptor status is a predictive biomarker. Previous studies have demonstrated that ER and/or PR expression is quite common in serous tumors of low malignant potential [35] and low-grade serous carcinomas [36]. Abu-Jawdeh found that 33 of 34 serous tumors of low malignant potential (94%) expressed ER [35]. Wong et al. found that the expression rates of ER (58%) and PR (43%) in low-grade serous carcinoma of the ovary were significantly higher than those in high-grade serous carcinoma (27% and 17%, respectively) [36].

In the present study, the median TTP of patients with ER+/PR+ tumors was longer than that of patients with ER+/PR- tumors; this difference approached statistical significance. Smyth et al. found that response to letrozole was more likely in patients with ovarian tumors with the highest level of ER expression [21], whereas a Gynecologic Oncology Group study found no difference in response to tamoxifen based on ER status [28]. Papadimitriou et al. reported that ER and PR expression status did not correlate with response to letrozole [31], and del Carmen et al. found that the time to treatment termination in patients with ER-/PR- disease was longer than that in patients with ER+/PR+ disease [20].

Other researchers have investigated the utility of ER and/or PR expression as a prognostic biomarker in ovarian cancer patients [37-43]. Only 2 of these studies restricted the sample to serous carcinomas of any histologic grade [42, 43]; the others included all ovarian cancer types and histologic grades. All but one of the studies [42] found that ER expression, PR expression, or ER/PR expression was prognostic. The prognostic value of ER, PR, or ER/PR expression in low-grade serous carcinoma was not a focus of the present study but is the subject of a future report.

Another aspect of this study that warrants further investigation is the long-term stability of ER or PR expression. In the present study, tumor tissue for ER and PR expression analysis was available from either the primary accession or in the recurrent setting. Breast cancer studies indicate varying levels of discordance of ER and/or PR expression between primary and recurrent tumors [44]. Furthermore, neoadjuvant chemotherapy may alter hormone

receptor status in breast cancer [45]. Thus, it will be important for future reports to precisely characterize the nature of the tumor (e.g., collected at primary surgery—ovarian or metastatic—or collected at relapse).

The present study had several potential limitations, including its retrospective and descriptive nature, selection and referral biases, relatively long study period, variety of hormonal drugs employed, and lack of a standard method for monitoring response. We attempted to minimize the influence of as many extraneous factors as possible by precisely defining the study population through eligibility criteria and applying clearly defined and stringent response criteria. As noted, of the 133 possible patient-regimens we reviewed, only 89 (67%) were included in the study.

The present study represents yet another example of our group's philosophy of studying specific rare ovarian/peritoneal carcinoma subtypes to overcome epithelial ovarian cancer's mask of the heterogeneity. Through the Rare Tumor Committee of the Gynecologic Oncology Group, separate trials have investigated several rare epithelial ovarian cancer subtypes, including low-grade serous carcinoma. The Gynecologic Cancer Intergroup also endorsed this approach in their recent consensus statement [46]. We believe that only with this strategy will advances be made in identifying more effective, biomarker-driven therapies for specific rare ovarian cancer subtypes. Thus, based on the hypothesis-generating data from this study, a phase II trial of an aromatase inhibitor in women with ER+ recurrent low-grade serous carcinoma of the ovary or peritoneum is warranted.

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Highlights

- Hormonal therapies have moderate anti-tumor activity in women with recurrent low-grade serous carcinoma of the ovary or peritoneum.
- Further study to determine whether ER/PR expression status is a predictive biomarker for this rare cancer subtype is warranted.
- Low-grade serous carcinoma of the ovary or peritoneum is a unique entity.

Table 1

Characteristics of 64 patients with recurrent low-grade serous carcinoma at the time of initial diagnosis

Characteristic	No. of patients (%)
Age at diagnosis, y	
Median	49.4
Mean	47.9
Range	19.0–73.6
Race	
White	52 (81.3)
Black	6 (9.4)
Hispanic	5 (7.8)
Other	1 (1.6)
Ever smoker	28 (43.8)
BMI at diagnosis,[1] kg/m^2	
Median	27.9
Mean	28.6
Range	17.0–45.3
Primary site	
Ovary	44 (68.8)
Peritoneum	20 (31.3)
Original histological subtype	
LMP	4 (6.3)
LG	60 (93.8)
Hormone receptor	
ER+/PR+	26 (40.6)
ER+/PR-	24 (37.5)
Not tested	14 (21.9)
FIGO stage	
IC	1 (1.6)
IIIA	4 (6.3)
IIIB	3 (4.7)
IIIC	47 (73.4)
IV	9 (14.1)

BMI, body mass index; LMP, low malignant potential; LG, low grade; ER, estrogen receptor; PR, progesterone receptor; FIGO, International Federation of Gynecology and Obstetrics

[1] Baseline data for 18 patients were unavailable.

Table 2

Response to hormonal therapy in order of administration, including chemotherapy and hormonal regimens

Order of regimen	CR	PR	SD	PD	Total
2	2	1	13	6	22
3	2	0	11	4	17
4	2	1	14	5	22
5	0	0	3	5	8
6	0	0	5	2	7
7	0	0	1	0	1
8	0	0	3	0	3
9	0	0	1	1	2
10	0	0	3	0	3
11	0	0	1	2	3
15	0	0	0	1	1
Total	6	2	55	26	89

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

Table 3

Hormonal therapy response of recurrent low-grade serous ovarian carcinoma by hormonal agent and platinum sensitivity status

Regimen	CR		PR		SD		PD		Total
	PSe	PRe	PSe	PRe	PSe	PRe	PSe	PRe	
Anastrozole	1	0	0	0	9	5	2	4	21
Fulvestrant	0	0	0	0	1	0	1	0	2
Letrozole	3	1	2	0	9	8	4	6	33
Leuprolide	0	0	0	0	5	1	1	1	8
Megestrol acetate	0	0	0	0	0	0	0	1	1
Tamoxifen	1	0	0	0	8	3	1	4	17
Raloxifene	0	0	0	0	1	0	0	0	1
Anastrozole + leuprolide	0	0	0	0	1	0	0	0	1
Letrozole + leuprolide	0	0	0	0	1	1	0	1	3
Tamoxifen + leuprolide	0	0	0	0	1	1	0	0	2
Total	5	1	2	0	36	19	9	17	89

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease ; PSe, platinum-sensitive; PRe, platinum-resistant

Table 4

Summary of complete and partial responses

Patient-regimen	Primary tumor site[1]	Regimen (No.)	Response		Platinum sensitivity status	CA 125 level, U/mL	
			Type	Duration, months		Start of regimen	End of regimen
1[2]	Peritoneum	Tamoxifen (4)	CR	117.6	Sensitive	64	27
2	Peritoneum	Anastrozole (2)	CR	112.2	Sensitive	99	25
3	Peritoneum	Letrozole (3)	CR	67.9	Sensitive	52	9
4	Peritoneum	Letrozole (4)	CR	52.2	Resistant	109	134
5	Ovary	Letrozole (3)	CR	11.9	Sensitive	12	37
6[2]	Peritoneum	Letrozole (2)	CR	42.0	Sensitive	8	6.4
7	Ovary	Letrozole (2)	PR	22.0	Sensitive	13	18.1
8[3]	Peritoneum	Letrozole (4)	PR	1.63	Sensitive	13	9.4

CA125, cancer antigen 125; ER, estrogen receptor; PR, progesterone receptor; CR, complete response; PR, partial response; NA, not available

[1] All patients had original histology of low-grade serous carcinoma

[2] No evidence of disease as of last contact

[3] Patient was responding to letrozole but stopped to enroll in a clinical trial of high-dose chemotherapy with autologous stem cell transplant.

Table 5

Eighty-nine patient-regimens by measurable disease and pre-treatment serum CA 125 categories and post-treatment serum CA 125 categories

	Response				
Pre-treatment CA 125 level	**CR**	**PR**	**SD**	**PD**	**Total**
≤35 U/ml					
No change[1]	2	2	10	4	18
>50% decrease	0	0	1	0	1
≤50% decrease	0	0	2	0	2
Overall increase	0	0	4	0	4
Total	2	2	17	4	25
>35 U/ml					
No change[1]	0	0	3	2	5
>50% decrease	4	0	9	1	14
≤50% decrease	0	0	15	4	19
Overall increase	0	0	11	15	26
Total	4	0	38	22	64
Total by response group	6	2	55	26	64

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

[1]Change in serum CA 125 ≤6 U/mL

Table 6

Univariate analysis of time to progression for 50 patients with known estrogen receptor (ER)/progesterone receptor (PR) status

Variable	No. of patients	HR	95% CI	p-value
Race				
White	40	-	-	-
Non-white	10	0.67	0.31–1.46	0.32
Site				
Ovary	36	-	-	-
Peritoneum	14	0.67	.34–1.34	0.26
Original diagnosis				
LG	47	-	-	-
LMP	3	1.20	.36–3.95	0.76
Smoking history				
Smoker	24	-	-	-
Non-smoker	26	0.75	0.42–1.36	0.34
Primary chemotherapy				
Adjuvant	44	-	-	0.66
Neoadjuvant	3	0.72	0.17–3.00	0.65
Hormone only	1	0.71	0.10–5.20	0.73
Adjvuvant+hormone	1	3.91	0.50–30.43	0.19
Neoadjvant+hormone	1	1.91	0.26–14.34	0.53
Platinum status				
Sensitive	30	-	-	-
Resistant	20	1.75	0.97–3.16	0.064
PR status				
PR+	26	-	-	-
PR-	24	1.80	0.98–3.30	0.056
ER/PR status				
ER+/PR+	26	-	-	-
ER+/PR-	24	1.80	0.98–3.30	0.056
BMI at time of diagnosis[1]				
18.5-24.9 (normal)	9	-	-	0.69
25-29.9 (overweight)	12	1.42	0.55–3.69	0.47
≥30 (obese)	15	1.0	0.41–2.41	0.99
Age at first hormonal therapy, years	-	-	-	<.001
<40	14	-	-	-
40-65	27	0.43	0.21–0.89	0.02
>65	9	3.08	1.23–7.72	0.017
Pre–hormonal therapy CA 125 level, U/mL				
≤35	20	-	-	-
>35	30	1.40	0.76–2.56	0.28

HR, hazard ratio; CI, confidence interval; LG, low grade; LMP, low malignant potential; BMI, body mass index; CA 125, cancer antigen 125

[1] BMI data for 14 patients were not available