A Phase II Evaluation of Goserelin and Bicalutamide in Patients With Ovarian Cancer in Second or Higher Complete Clinical Disease Remission

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Supported by Grants OvPPG CA-52477 and K23 CA-89333, The Eileen Genet Fund, the Ovarian Cancer Research Fund, and Astra-Zeneca.

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Received May 21, 2007; revision received July 5, 2007; accepted July 10, 2007.

BACKGROUND. The current study was conducted to determine the effect of goserelin and bicalutamide on progression-free survival (PFS) in patients with epithelial ovarian cancer who were in second or greater complete disease remission.

METHODS. Patients received bicalutamide at a dose of 50 mg orally daily and goserelin at a dose of 3.6 mg subcutaneously every 4 weeks. CA 125 was obtained monthly, with computed tomography performed every 3 months. Correlative studies included serum luteinizing hormone, follicle-stimulating hormone, vascular endothelial growth factor, free testosterone, and androstenedione and the germline polymorphisms CYP19A1 and androgen receptor.

RESULTS. Between October of 2000 and October of 2002, 35 patients were enrolled. Three patients (9%) received therapy at the time of first disease remission and were removed from the study, and 1 patient (3%) was removed for liver function test abnormalities. The most frequent toxicities were grade 1 alkaline phosphatase (54%), fatigue (57%), and hot flashes (42%) based on the National Cancer Institute common toxicity scale, version 2.0. The PFS for patients receiving protocol therapy in second disease remission (21 patients) was 11.4 months (95% confidence interval [95% CI], 10.2–12.6 months). The PFS for patients receiving protocol therapy in third or fourth disease remission (11 patients) was 11.9 months (95% CI, 10.8–14.1 months). The percentage of patients remaining in second disease remission at given times are: 100% at 3 months, 100% at 6 months, 72% at 9 months, 47% at 12 months, 28% at 15 months, 22% at 18 months, 19% at 21 months, and 13% at 24 months. There were no associations noted between androgen receptor repeat number, genotype, allelotype, or haplotypes and PFS.

CONCLUSIONS. The use of goserelin and bicalutamide did not appear to prolong PFS in patients with epithelial ovarian cancer in second or greater complete disease remission. The number of patients in disease remission at given time points may serve as a clinical trial endpoint for future studies of consolidation therapy. ***Cancer* 2007;110:2448–56.** © *2007 American Cancer Society.*

KEYWORDS: ovarian cancer, consolidation therapy, androgen blockade, survival.

In patients with advanced ovarian cancer, aggressive optimal surgical debulking and platinum therapy with primary taxane therapy are reported to result in a median overall survival of >5 years, but the long-term cure rate remains in the range of 20% to 30%.[1,2] For patients with recurrent disease, subsequent and repeated chemotherapy responses are often observed with decreasing durations of disease control until broad chemotherapy resistance develops.[3] Opportunities to improve the outcome for patients exist if primary therapy is made more effective, or by applying effective targeted

DOI 10.1002/cncr.23072
Published online 4 October 2007 in Wiley InterScience (www.interscience.wiley.com).

"consolidation" or "maintenance" approaches to patients in complete primary or subsequent disease remission.[4]

A variety of hormones influence ovarian function, although their role in ovarian carcinogenesis has been controversial.[5–7] Several studies have demonstrated the predominance of androgen receptor (AR) (present in 67–96% of cases) over estrogen receptor (ER) (present in 32–55% of cases) and progesterone receptor (PR) (present in 46–52% of cases) in ovarian carcinoma.[8–11] Plasma concentrations of androgens are greater than those of estrogens during the late follicular phase of the menstrual cycle[12] and in the postmenopausal ovary, in which 15-fold higher concentrations are noted in the ovarian vein compared with peripheral vein serum.[13] Some studies have shown that patients with ovarian cancer have higher levels of circulating androgens before the diagnosis of cancer is made than are found in women without cancer[14]; others have refuted this finding.[15] Gonadotropin receptors also have been shown to be expressed in at least 50% of ovarian surface epithelial cells.[16] In animal studies in F1-Wx/Wv mice, which normally uniformly develop bilateral complex tubular adenomas correlated with a 4-fold increase in follicle-stimulating hormone (FSH) and luteinizing hormone (LH), treatment with goserelin versus placebo resulted in the significant suppression of gonadotropins ($P = .0005$) and no tumor development ($P = .00005$).[17] Finally, recent data have shown the importance of the suppression of vascular endothelial growth factor (VEGF) in regulating ovarian cancer growth.[18,19] Moreover, it has been suggested that loss of ovarian function promotes tumorigenesis by resulting in increased gonadotropins, which promote vascularization via increased levels of VEGF.[20] Recent data also have supported the finding that testosterone replacement in castrated rats increases mRNA levels of VEGF.[21]

This phase 2 study evaluated the hypothesis that the inhibition of the androgen axis could result in a decrease in tumor recurrence by inhibiting AR, reducing circulating gonadotropins, and suppressing androgen-mediated VEGF production. Patients with ovarian cancer in disease remission received goserelin (a gonadotropin-releasing hormone analogue) and bicalutamide (an oral nonsteroidal antiandrogen), with progression-free survival (PFS) as the primary endpoint and correlative studies characterizing androgens, AR, and coregulators as secondary endpoints.

MATERIALS AND METHODS

Inclusion/Exclusion Criteria

Eligible patients had 1) histologic confirmation of epithelial ovarian, primary peritoneal, or fallopian tube cancer at the time of diagnosis; 2) undergone initial surgical cytoreduction and chemotherapy with at least 1 platinum-containing regimen; 3) failure of the primary regimen as manifested by recurrent disease; and 4) were in a complete clinical disease remission (CR) after additional chemotherapy or surgery. Complete clinical remission was defined as a CA 125 level $\leq$35 U/mL, negative physical examination, and no definite evidence of disease by computed tomography (CT) scan. Lymph nodes and/or soft-tissue abnormalities measuring $\leq$1.0 cm are often present and may not be considered definite evidence of disease. Patients were permitted to have entered a second or any subsequent clinical CR. Patients had to have a Karnofsky performance status (KPS) $\geq$60% and adequate organ function (defined as an absolute neutrophil count $\geq$1500/μL, a platelet count $\geq$100,000/μL, total bilirubin and serum creatinine $\leq$1.5 times the institutional upper limit of normal, and aspartate aminotransferase and alkaline phosphatase levels $\leq$2.5 times the institutional upper limit of normal). Patients were excluded from the study if they had received any investigational drug or radiotherapy during the 4 weeks before study entry, or had any uncontrolled cardiac, pulmonary, metabolic, renal, gastrointestinal, infectious disease, or other history that placed them at an unacceptable risk for participation in the study. The therapeutic use of warfarin was not permitted.

Treatment Plan

The pretreatment evaluation included history and physical examination, assessment of KPS, complete blood cell count, hepatic function profile, serum creatinine, serum CA 125 level, electrocardiography, and CT scan. During treatment, patients were evaluated monthly with physical examination, and all laboratory studies were repeated. CT scan was repeated every 3 months or sooner at the discretion of the investigator if disease progression was suspected. Bone density was assessed within 6 months of the initiation of the study, and yearly while the patient remained on study.

Patients received bicalutamide at a dose of 50 mg orally continually, and goserelin was administered at a dose of 3.6 mg subcutaneously every 4 weeks. No dose interruptions or modifications were performed for grade 1 or grade 2 hematologic toxicity or grade 1 nonhematologic toxicity. Patients were removed from study for any hematologic toxicity of $>$ grade 3, unacceptable $\geq$ grade 2 nonhematologic toxicity, or at patient request.

Correlative Studies

Peripheral blood (20 mL) was obtained at baseline to measure VEGF, FSH, LH, free testosterone, androste-

nedione, and estradiol levels. Repeated measurements were obtained every 12 weeks and at the time of treatment failure. Germline DNA was extracted from peripheral blood lymphocytes using standard laboratory techniques. The trinucleotide CAG repeats in exon 1 of *AR* was amplified using previously published primers.[22] The short, long, and mean numbers of repeats were calculated and evaluated for associations with PFS. The transcriptional transactivation function of the AR protein in vitro is correlated inversely with the length of the polyglutamine tract encoded by this repeat.[23,24]

Genotypes for 4 single nucleotide polymorphisms (SNPs) (rs4646, rs10046, rs2414096, and rs727479) in *CYP19A1* were determined. These haplotype-tagging SNPs are representative of approximately 90% of the genetic variation in the coding region of *CYP19A1*. Recent data indicate that these haplotypes are associated with circulating hormone levels.[25,26] Genotyping was performed using a TaqMan allelic discrimination assay detected on an ABI prism 7900 sequence detection system (Applied Biosystems, Foster, Calif) with high-fidelity reagents. The genotype completion rate was 95%. Bayesian statistical methods were used to reconstruct haplotypes from diploid genotype data. This methodology was performed using the PHASE program (version 2.1) by Stephens et al.[27,28] Single loci genotypes and haplotypes were compared with patient outcome using the Fisher exact and log-rank tests. All statistical tests were 2-sided.

Tissue blocks were requested to obtain unstained slides. Representative slides of malignant tissue (from formalin-fixed, paraffin-embedded blocks) were stained via immunohistochemistry for AR, PR, and ER. Standard immunoperoxidase techniques were used by the core facility at the Memorial Sloan-Kettering Cancer Center as outlined in the laboratory procedures manual (1995 revision). Slides were reviewed by the investigating pathologist (K.P.). A semiquantitative method of scoring the staining pattern was used. Staining intensity was recorded as weak (W), moderate (M), or strong (S). The quantity of staining was expressed as a percentage of the tumor with $\geq$5% staining considered to be positive.

Study Endpoints

The endpoint of the current study was PFS. PFS was defined based on the data from Rustin et al.[29] Treatment failure was characterized by 1) evidence of tumor recurrence on physical examination or 2) radiographic evidence of disease recurrence using RECIST (Response Evaluation Criteria In Solid Tumors) criteria. Patients were removed from the study at the time of treatment failure.

All patients provided written informed consent. The protocol was approved by the institutional review board annually.

Statistical Considerations

The objective of the current study was to estimate the PFS for this intervention with the administration of subcutaneous goserelin and oral bicalutamide in patients in second or greater CR. The second PFS was measured as the interval from the initiation of secondary therapy to the date of the second disease recurrence (PFS2). The third or fourth PFS was measured as the interval from the initiation of the third or fourth therapy to the date of the third or fourth disease recurrence (PFS3 or PFS4). PFS (protocol) was defined as the time from the protocol start date to disease progression or last follow-up for the patients who did not develop disease progression. PFS intervals were reported in months. The first PFS (preprotocol intervention) was measured as the time interval from the initiation of primary therapy to the date of first disease recurrence (PFS1).

Historically, in the group of patients with a second or greater CR, the median PFS2 is 9 months to 10 months.[30] We planned to accrue 35 patients at an accrual rate of 3 patients per month, with follow-up after accrual for an additional 2 years. A minimum follow-up of 18 months was required to enable us to estimate the median time to disease recurrence with a 95% confidence interval (95% CI) given by $\pm$ 4.5 months. This degree of improvement was selected arbitrarily as clinically meaningful. The 95% CI was computed under the exponential survival model. We would examine the treatment further if we observed a median of $>$13.5 months.

RESULTS

Patient Characteristics

Thirty-five patients were enrolled in the study from October of 2000 to October of 2002 as described in Table 1. The median age of the patients was 53 years (range, 41–70 years) with a median KPS of 90% (range, 80–100%). The majority of patients had stage III (80%) or stage IV (11%) disease at the time of diagnosis, according to the TNM staging system. The majority of patients (74%) underwent an initial optimal surgical cytoreduction. The majority had papillary serous (86%) or endometrioid (9%) histology, with a minority having clear cell (5%) histology. All patients received taxane and platinum-based primary chemotherapy. Twelve patients (34%) underwent second-look assessment and 13 patients (37%) received additional consolidation therapy. Twenty-three patients

TABLE 1
Patient Characteristics (n = 35)

Median age (range), y	53 (41–70)
Median KPS	90 (80–100%)
Stage	
I	3 (9%)
III	28 (80%)
IV	4 (11%)
Size of residual at primary tumor debulking, cm	
Optimal (≤1)	26 (74%)
Suboptimal (>1)	9 (26%)
Second-look assessment	
Not performed	23 (66%)
Negative	5 (14%)
Microscopic	6 (17%)
Macroscopic (≤1 cm)	1 (3%)
Recurrence surgery	
Yes	12 (34%)
No	23 (66%)
No consolidation therapy	22 (63%)
iv or ip consolidation therapy	13 (37%)
First remission (persistent)	3 (8%)
Second remission	21 (60%)
Third remission	9 (26%)
Fourth remission	2 (6%)

KPS indicates Karnofsky performance status; iv, intravenous; ip, intraperitoneal.

TABLE 2
Treatment Toxicities

Adverse events (n = 32)	Maximum grade per patient*			
	1	2	3	4
Alkaline phosphatase elevation	19	0	0	0
Back pain	1	0	0	0
Bloating	1	0	0	0
Bone pain	1	0	0	0
Constipation	6	0	0	0
Dermatologic/rash	2	0	0	0
Diarrhea	1	0	0	0
Dizzy	2	0	0	0
Dry skin	3	0	0	0
Fatigue	19	3	0	0
Headaches	5	0	0	0
Anemia	5	1	0	0
Hot flashes	15	1	0	0
Vagina	6	1	0	0
AST elevation	2	0	0	0
ALT elevation	3	1	0	0
Total bilirubin elevation	2	0	0	0

AST indicates aspartate aminotransferase; ALT, alanine aminotransferase.
* Based on the National Cancer Institute common toxicity scale, version 2.0.

(66%) underwent a surgical procedure at the time of disease recurrence. The majority of patients were enrolled on protocol in second CR (60%), with other patients enrolling in third (26%) or fourth (6%) CR. Three patients (9%) received protocol therapy in first disease remission after disease persistence and were excluded from analysis. The median time from the last administration of chemotherapy to the initiation of protocol therapy was 1.6 months (range, 0.4–15.4 months). The median time on protocol therapy was 5 months (range, 5–24 months).

Treatment Toxicities

Three patients (9%) were treated in first disease remission and were removed from the analysis. One patient (3%) was removed from treatment due to toxicity (patient choice secondary to grade 2 elevated liver function tests), 28 patients were removed for disease progression, 1 patient was removed for newly diagnosed breast cancer, 1 patient withdrew consent, and 1 patient completed the planned 24 months of therapy and ended treatment in disease remission. Treatment was generally well-tolerated with no grade 3 or 4 toxicities attributed to protocol treatment. Grade 2 toxicities occurred in only a few patients as outlined in Table 2: fatigue (8%), hemoglobin (3%), hot flashes (3%), vaginal dryness (3%), and geranyl-geranyl protein transferase type II (GGPT) elevation (3%). The majority of toxicities were grade 1, with the most common being an elevation in the alkaline phosphatase level (54%), fatigue (57%), and hot flashes (43%). Bone density examination was performed at baseline and every 6 months while the patient received treatment. Considered categorically, baseline bone density scores were normal (17%), osteopenia (63%), and osteoporosis (20%). Seventeen patients had at least 1 follow-up study (6 months on study), and 1 of 17 had a decline in bone density by 1 category.

Primary Treatment Endpoint: PFS

The PFS for patients receiving protocol therapy in second disease remission (PFS2) (21 patients) was 11.4 months (95% CI, 10.2–12.6 months). The PFS for patients receiving protocol therapy in third or fourth disease remission (PFS3 or 4) (10 patients) was 11.9 months (95% CI, 10.8–14.1 months). The PFS from the start of protocol therapy or PFS (protocol) was 4.6 months (95% CI, 3.0–5.7 months) (Table 3).

The PFS (PFS1) for all evaluable patients on protocol (prestudy intervention) was 21.7 months (95% CI, 16.1–31.4 months).

Exploratory Endpoints

For patients receiving protocol therapy in second disease remission only (21 patients), 3 patients (14%) had a PFS2 > PFS1, with differences of 2.9 months, 15.4 months, and 38.6 months, respectively, as illu-

TABLE 3
Treatment Outcome: Duration of PFS

Patients Treated in PFS2, 3, or 4 (n = 32)	
PFS1 (preprotocol therapy)	21.7 mo (95% CI, 16.1–31.4 mo)
PFS2	11.8 mo (95% CI, 10.4–13.2 mo)
PFS3 or 4 (n = 10)	11.9 mo (95% CI, 10.8–14.1 mo)
Patients treated in PFS2 only (n = 21)	
PFS1	22.9 mo (95% CI, 16.1–31.4 mo)
PFS2	11.4 mo (95% CI, 10.2–12.6 mo)

PFS indicates progression-free survival; PFS1, time interval from the initiation of primary therapy to the date of first disease recurrence; 95% CI, 95% confidence interval; PFS2, PFS for patients receiving protocol therapy in second disease remission; PFS3 or 4, PFS for patients receiving protocol therapy in third or fourth disease remission.

strated in Table 4. None of these 3 patients underwent secondary surgery at the time of disease recurrence.

Table 5 describes the patients receiving protocol therapy in second CR or greater and remaining disease free at given time points. The proportion of patients remaining in second disease remission among the 32 patients in second or greater CR versus time is as follows: 100% at 3 months, 100% at 6 months, 72% at 9 months, 47% at 12 months, 28% at 15 months, 22% at 18 months, 19% at 21 months, and 13% at 24 months. Figure 1 shows the PFS curves for all patients treated in second or greater CR (Fig. 1A), and depicts the group treated in second CR separately (Fig. 1B).

Immunohistochemistry

Nineteen patients (54%) had tumor blocks adequate to obtain unstained slides for immunohistochemistry. The results of AR, ER, and PR staining are shown in Table 6. Eleven of 19 patients (58%) demonstrated AR expression (defined as weak or strong and $\geq$5% of cells with receptor), 14 patients (74%) demonstrated PR expression, and 10 patients (53%) demonstrated ER expression. Only 6 of the tested patients (21%) were found to have all 3 receptors present.

Serum Levels of LH, FSH, and VEGF

Serum levels of LH, FSH, androstenedione, and VEGF are summarized in Figure 2 as boxplots. The levels of LH and FSH were uniformly suppressed in all patients by the second month. Variability in VEGF levels between patients is illustrated, but VEGF suppression was not noted in treated patients. Testosterone and androstenedione levels were low at the time of study entry, and no further changes could be observed.

Germline Polymorphisms in AR and CYP1A1

PFS was compared with the *AR* short, long, and mean trinucleotide repeat number. PFS was modeled as a continuous variable with censoring as appropriate and also as a dichotomous outcome using a PFS of 15 months as a cutoff point for the time-specific PFS rate. There were no associations noted between *AR* repeat number and any metric of PFS. Genotype, allelotype, and haplotype analyses were performed in a similar manner for *CYP19A1*. There were no associations found between single loci testing or haplotypes and any metric of PFS.

TABLE 4
Exploratory Outcome: Patients with PFS2 > PFS1 Treated in PFS2 (n = 21)

Patient no.	Duration of PFS1, months	Duration of PFS2, months	Difference, months
11	9.6	12.5	2.9
29	23.9	39.3	15.4
30	22.9	61.5	38.6

PFS indicates progression-free survival; PFS2, PFS for patients receiving protocol therapy in second disease remission; PFS1, time interval from the initiation of primary therapy to the date of first disease recurrence.

TABLE 5
Exploratory Outcome: Percentage of Patients in CR at Given Time Intervals

Time interval, months	PFS1 rate among patients in CR2, % (PFS1 rate among patients in CR ≥2), %	PFS2 rate among patients in CR2, % (PFS2 rate among patients in CR ≥2), %
3	100 (100)	100 (100)
6	100 (100)	100 (100)
9	100 (100)	71 (72)
12	86 (84)	38 (47)
15	76 (72)	29 (28)
18	62 (59)	24 (22)
21	52 (50)	19 (19)
24	43 (41)	14 (13)

CR indicates complete disease remission; PFS indicates progression-free survival; PFS1, time interval from the initiation of primary therapy to the date of first disease recurrence; CR2, second complete disease remission; PFS2, PFS for patients receiving protocol therapy in second disease remission.

DISCUSSION

There is significant interest in investigating nontoxic consolidation or maintenance therapeutic strategies for patients with ovarian cancer in both primary and secondary CR. Recent clinical data support the modest efficacy of aromatase inhibition in preselected ER-positive patients with ovarian cancer, supporting a possible role for hormonal manipulation.[31] Likewise, the hypothesis that the inhibition of the andro-

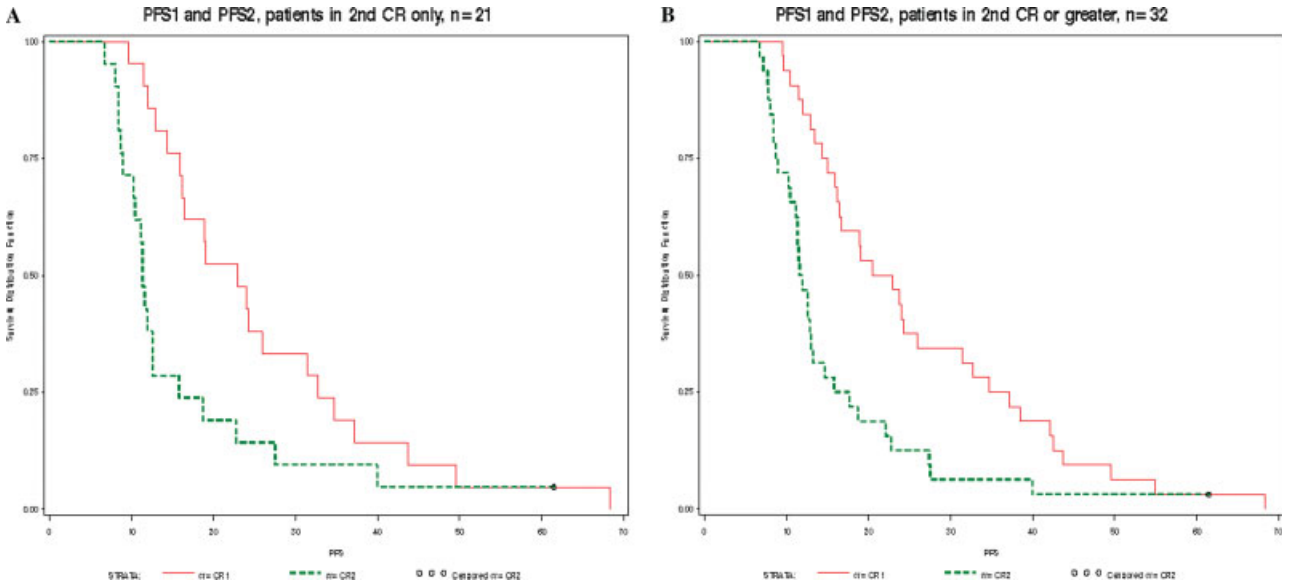

FIGURE 1. Progression-free survival (PFS) curves for (A) all patients treated at the time of second complete remission (CR2) and (B) those treated in CR2 or greater. PFS1 indicates the time interval from the initiation of primary therapy to the date of first disease recurrence; PFS2, intervals from initiation of secondary therapy to second disease recurrence.

gen axis could result in a decrease in tumor recurrence by inhibiting AR, thereby reducing circulating gonadotropins, and by suppressing androgen-mediated VEGF production was soundly formulated from preclinical data.[8,12,14,16,17,21] The use of goserelin and bicalutamide was found to be well-tolerated, with the majority of toxicities reported as grade 1 or grade 2. Only 1 patient was discontinued from the study because of toxicity. With regard to the primary efficacy endpoint, the intervention did not increase the PFS to the predetermined value of 16.5 months necessary for considering this approach worthy of further study. Although not effective as a disease remission maintenance strategy, it should be noted that gonadotropin-releasing hormone analogs have demonstrated variable activity for patients with measurable disease, with responses ranging from 12.5% (PFS of 8.7 months) to 4.3%, a small proportion of patients with stable disease, and minimal toxicity.[32–34] Recognizing the modest activity of generally short duration, it still may be reasonable to use this or other hormonal strategies in patients with measurable disease who have no other more effective options remaining, and who have a favorable toxicity profile. However, current study data suggest that further investigation of gonadotropin-releasing hormone analogs as a consolidation strategy is not warranted.

A lack of efficacy in prolonging disease remission was noted despite the finding that the majority of patients (58%) had positive AR staining by immunohistochemistry; this finding is in keeping with previously published data.[8–11] No association was observed between the presence of AR and outcome. AR and CYP19A1 polymorphisms were examined both as single loci and haplotypes and were not found to be associated with PFS. These results are considered

TABLE 6
Immunohistochemistry (AR, PR, and ER)*

Patient no.	AR	PR	ER
2	W 60%	M <5%	W 90%
5	W 10%	S <5%	0
7	0	M 10%	0
9	M 40%	S 30%	M 10%
10	0	M <5%	0
11	M 50%	S 20%	W 80%
13	0	M <5%	W 30%
14	W 50%	S <5%	0
16	S 50%	S <5%	0
18	M 50%	S <5%	W 30%
20	0	M 10%	W 20%
22	M 90%	S 10%	W<5%
23	M 50%	S 20%	S 70%
24	W 80%	X	0
25	0	S 10%	M 10%
27	W<5%	M <5%	0
30	0	M <5%	0
31	0	W <5%	W<5%
36	0	W 20%	W 20%

AR indicates androgen receptor; PR, progesterone receptor; ER, estrogen receptor; W, weak; M, moderate; S, strong; X, sample unsatisfactory for analysis.

* Tissue blocks were available in 19 of 35 patients with which to prepare unstained slides for immunohistochemical analysis.

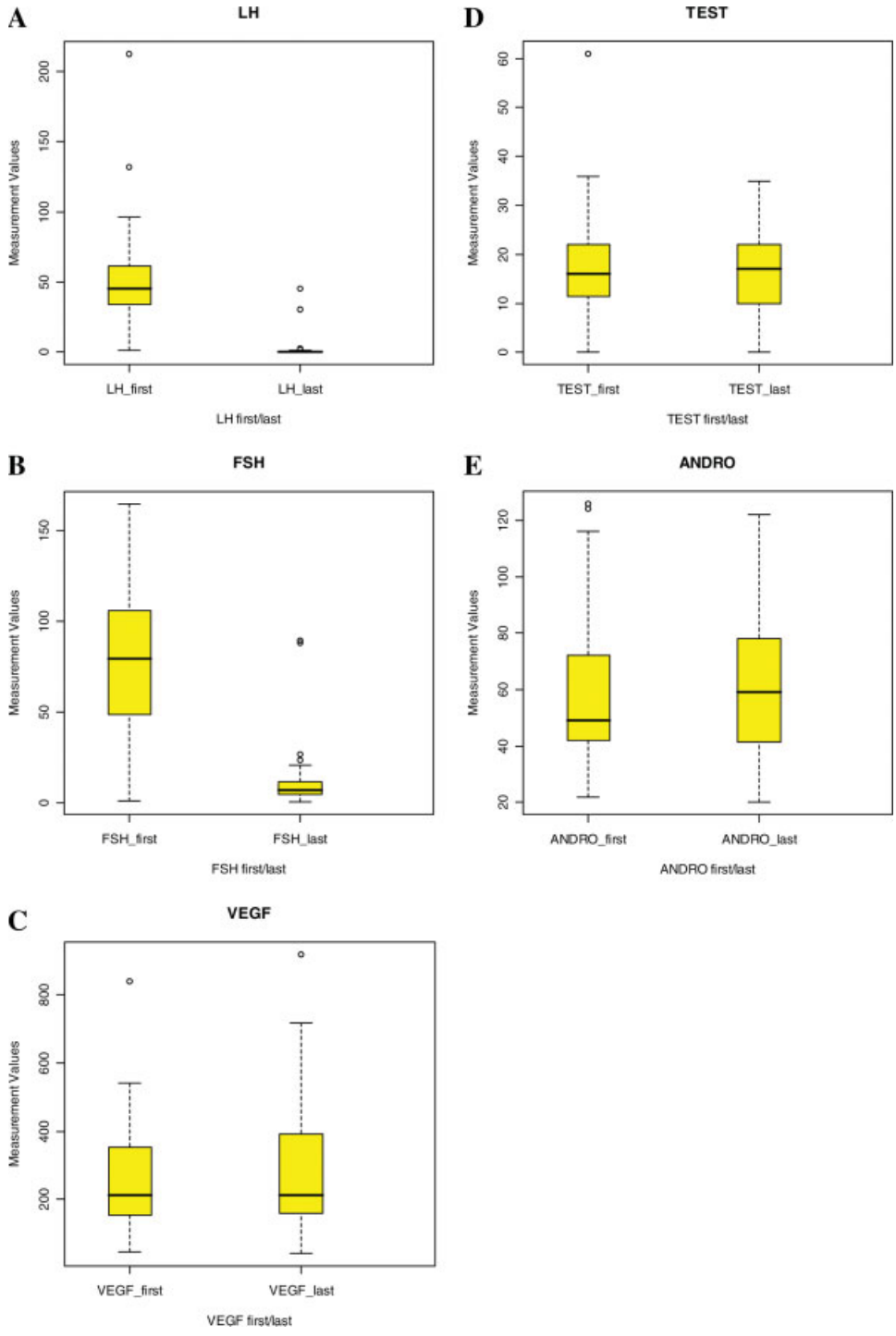

FIGURE 2. Serum levels of (A) luteinizing hormone (LH; in mIU/mL), (B) follicle-stimulating hormone (FSH; in mIU/mL), (C) vascular endothelial growth factor (VEGF; in pg/mL), (D) testosterone (TEST; in ng/dL), and (E) androstenedione (ANDRO; in ng/dL).

exploratory; we recognize the limitations imposed by the small sample size and reasonable narrow range of progression-free outcomes in the current study.

Suppression of LH and FSH was observed in all patients as expected because of the known effect of the gonadotropin-releasing hormone analogue. VEGF levels were found to have considerable interpatient variability and did not exhibit decreases as a result of suppression of the androgen axis, as hypothesized.[20]

Several additional observations can be drawn from this study. With regard to our patient population, we demonstrated that sufficient numbers of patients do return to CR (all of whom did so after platinum-based reinduction chemotherapy) to justify the study of interventions with the goal of prolonging disease remission. We learned that not restricting the study population to those in second CR results in patients receiving the intervention at the third and sometimes fourth CR timepoints, which unnecessarily complicates the analysis. For future studies, we recommend restricting patients to second CR. Furthermore, having no time restriction with regard to when patients begin protocol therapy once CR is reached resulted in a short median time from last chemotherapy of 1.6 months, but ranged from 0.4 to 15.4 months. For comparisons with the literature, it is necessary to report PFS2 or PFS3 as the time from the initiation of chemotherapy to disease progression. For future studies, we will institute an eligibility criterion requiring patients to enter the study within 4 months of their disease returning to CR.

Because the majority of patients in the current study (21 patients) received protocol therapy in second CR, we considered them separately as well as part of the total patient population. The use of goserelin and bicalutamide resulted in a PFS2 of 11.4 months in this cohort of patients treated at the time of second CR, and this is within the range of patients reported in the literature who were treated at the time of second disease recurrence and followed with observation.[35]

Recent data have suggested that a simple determination of the median PFS may not be the most suitable endpoint for consolidation trials. Other suggested endpoints have included the proportion of patients achieving a second CR that is longer than the first,[3] or patients continuously in CR at given time points.[36] In our study, 3 of 21 patients with a second CR had a second CR that was longer than the first (14%), with 2 of these patients (9.5%) having clinically meaningful differences. This fits with previously published data that second CRs are infrequently longer than the first, and that these protocol-treated patients are similar to those who are observed. No unique features could be identified among the 3 patients with a second CR that was longer than the first (none had undergone secondary surgery), and there were no detectable differences noted in hormone levels. AR was not present in any of these patients. Finally, the percentage of patients in CR at different time points is reported, and this may serve as a potential benchmark for subsequent studies once validation using a larger observed dataset is performed.

The use of goserelin and bicalutamide did not appear to prolong the PFS of patients with epithelial ovarian cancer in a second or greater CR. The number of patients with a second CR that was longer than the first remained infrequent. The number of patients remaining in CR at given timepoints is reported herein and may serve as a clinical trial endpoint for future consolidation studies if validated in sufficient numbers of patients.

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