Antiestrogen Therapy Is Active in Selected Ovarian Cancer Cases: The Use of Letrozole in Estrogen Receptor–Positive Patients

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Abstract

Purpose: To evaluate the efficacy of the aromatase inhibitor letrozole in preselected estrogen receptor (ER)–positive relapsed epithelial ovarian cancer patients and to identify markers that predict endocrine-sensitive disease.

Experimental Design: This was a phase II study of letrozole 2.5 mg daily until clinical or marker evidence of disease progression in previously treated ER-positive ovarian cancer patients with a rising CA125 that had progressed according to Rustin's criteria. The primary end point was response according to CA125 and response evaluation criteria in solid tumors (RECIST) criteria. Marker expression was measured by semiquantitative immunohistochemistry in sections from the primary tumor.

Results: Of 42 patients evaluable for CA125 response, 7 (17%) had a response (decrease of >50%), and 11 (26%) patients had not progressed (doubling of CA125) following 6 months on treatment. The median time taken to achieve the CA125 nadir was 13 weeks (range 10-36). Of 33 patients evaluable for radiological response, 3 (9%) had a partial remission, and 14 (42%) had stable disease at 12 weeks. Eleven patients (26%) had a PFS of >6 months. Subgroup analysis according to ER revealed CA125 response rates of 0% (immunoscore, 150-199), 12% (200-249), and 33% (250-300); $P = 0.028$, χ^2 for trend. Expression levels of HER2, insulin-like growth factor binding protein 5, trefoil factor 1, and vimentin were associated with CA125 changes on treatment.

Conclusions: This is the first study of a hormonal agent in a preselected group of ER-positive ovarian cancer patients. A signature of predictive markers, including low HER2 expression, predicts response.

Ovarian cancer is the fifth most common cause of female cancer death in the United States (1). The majority of patients present with disease spread beyond the pelvis. Despite surgical debulking and platinum/taxane combination chemotherapy, the median progression-free survival (PFS) in these patients is only 11 to 18 months, with a median overall survival (OS) of 24 to 38 months (2, 3). Relapsed disease is often detected on the basis of a rising serum CA125 before the development of significant clinical symptoms. The optimal management of these patients is unclear. There is no proven survival advantage to initiating chemotherapy in asymptomatic patients so many centers adopt a watchful waiting policy. Evaluation of agents with low toxicity can be done in this setting.

Endocrine therapies have proved invaluable in the treatment of adjuvant and metastatic breast cancer, but their use has not been adequately assessed in ovarian cancer. In postmenopausal women, circulating estrogens are derived primarily from the aromatization of estrogen precursors by the aromatase enzyme in peripheral tissues. Ovarian cancer occurs in a similar population of peri- and postmenopausal women as those with breast cancer, and the majority of primary ovarian tumors express estrogen receptors (ER; ref. 4). In our laboratories, we have studied growth-inhibitory effects of estrogens in ovarian cancer model systems and shown that this is strongly related to ER expression. It would be predicted from these observations that the ovarian cancers with the highest ER levels are likely to be the most responsive to endocrine therapies (5, 6). Studies of estrogen-regulated proteins have indicated that a number of secondary markers are likely to be differentially expressed in responding tumors (6–8). Using cDNA microarray analysis and quantitative reverse transcription-PCR, we have recently

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identified a series of genes that are regulated by estrogen in ER-positive ovarian cancer cells in culture, and these included trefoil factor 1 (TFF1/pS2), insulin-like growth factor binding protein 5 (IGFBP5), and vimentin (9). TFF1 expression is up-regulated by 17β-estradiol (E_2), whereas IGFBP5 and vimentin are down-regulated.

Letrozole is a potent nonsteroidal aromatase inhibitor. In studies of postmenopausal women, letrozole rapidly suppressed circulating estrogen levels by >98.9% (10). Between 1998 and 2000, we conducted a study to test the efficacy of letrozole in unselected patients with relapsed ovarian cancer (11). A CA125 response was seen in 5 out of 54 evaluable patients, and marker stabilization was noted in a further 14 patients. By Union Internationale Contra Cancer (UICC) criteria, there were no cases of partial remission (PR); however, disease stabilization of >12 weeks was noted in 10 patients (median time to progression in this group was 35 weeks; range, 22-87 weeks). Tumors from both the UICC stable and CA125 stable/responders groups had significantly higher ER ($P = 0.027$ and 0.013, respectively). In addition, increased expression of HER2 was associated with a decreased likelihood of CA125 response or stabilization. These data suggested an "endocrine-sensitive subgroup" of ovarian cancer with ER histoscore cutoff of ≥150. On the basis of these findings, the present study was initiated, recruiting patients with relapsed ovarian cancer whose tumor expressed ER with a histoscore of ≥150. The aims of this study were to validate the efficacy of letrozole in this preselected population of patients and to identify predictive markers that would help to further identify the subgroup of patients with endocrine-sensitive disease.

Materials and Methods

Study design. This was an investigator-initiated, single-arm, prospective phase II study of letrozole 2.5 mg p.o. daily in patients with relapsed ovarian cancer whose primary tumor expressed the ER with a histoscore of 150 or greater.

Eligibility. Relapsing patients were evaluable on the basis of a rising CA125, with progressive disease as defined by Rustin's criteria [ref. 12; CA125 greater than twice the upper limit of normal (ULN) or greater than twice nadir following previous chemotherapy if the CA125 did not normalize during this treatment]. Patients were eligible for the study if they also met the following criteria: histologically proven ovarian or primary peritoneal carcinoma, prior surgery, and at least one prior systemic chemotherapy regime, but no prior endocrine therapy, postmenopausal or previous bilateral oophorectomy, primary tumor specimen available for measurement of markers, age ≥18, Eastern Cooperative Oncology Group (ECOG) performance status 0-2, life expectancy >3 months, creatinine <1.5 × ULN, bilirubin <1.5 × ULN, transaminases and alkaline phosphatase <2.5 × ULN, WBC ≥3×10^9/L, neutrophils ≥1.5×10^9/L, platelets ≥100×10^9/L, hemoglobin ≥9 g/dL. Patients with any of the following conditions were ineligible for the study: tumors of borderline malignancy, prior systemic treatment within 4 weeks of study entry, concurrent use of an investigational drug, bowel obstruction or malabsorption, ascites requiring multiple drainages or ascites drained within 30 days of study entry. Approval for the study was obtained from the Local Research Ethics Committees, and all patients gave written consent before participating. Entry into the study required an ER histoscore of >150, and these were assessed by one gynecologic pathologist (A.R.W.W.) within a single Pathology Department.

Pretreatment evaluations. The baseline evaluations included history, physical examination (including pelvic examination), ECOG performance status, baseline assessment of toxicity, abdominal and pelvic computed tomography (CT) or magnetic resonance imaging scan, full blood count, serum chemistries and electrolytes, and serum CA125 level.

Treatment regimen. Treatment with letrozole (2.5 mg p.o. daily) continued until evidence of disease progression as defined by doubling of CA125 from pretreatment baseline or evidence of clinical or radiological progression. No dose modification was permitted.

Evaluation during therapy. ECOG performance status assessment, clinical examination, toxicity assessment, and CA125 measurement were done every 4 weeks during letrozole treatment. CT scans of the abdomen and pelvis were done in all patients before study entry and every 12 weeks thereafter.

Response and toxicity criteria. Radiological response to therapy was assessed according to response evaluation criteria in solid tumors (RECIST).

Response according to CA125 was defined to have occurred if either of Rustin's criteria (13) were fulfilled: (*a*) 50% response; if there was a 50% decrease in serum CA125 levels, from two initially elevated samples, then a 50% response had occurred. The sample showing a 50% decrease must have been confirmed by a fourth sample (i.e., requires four samples); (*b*) 75% response; if there had been a serial decrease in CA125 levels of more than 75% over 3 samples, then a 75% response had occurred (i.e., requires three samples). In both 50% and 75% response definitions, the final sample had to be analyzed at least 28 days after the previous sample.

Disease progression according to CA125 criteria was defined to have occurred if the CA125 level increased to greater than or equal to twice the pretreatment CA125 value (12, 13). Doubling had to be confirmed by a second sample.

Predictive marker analysis. One representative formalin-fixed, paraffin-embedded block of tumor tissue was selected by the pathologist after a review of histology of all slides of the primary resection. Sections (3 μm) were cut from the block, deparaffinized and rehydrated. Endogenous peroxidase activity was blocked by incubating sections in 3% H_2O_2. For detection of ER, sections were pressure cooked for 3 min at full pressure in citrate buffer (0.01 mol/L; pH 6.0). For detection of HER2, IGFBP5, and vimentin, sections were immersed in citrate buffer (0.005 mol/L; pH 6.0) and microwaved for 3 × 5 min. For TFF1, sections were treated with 0.0025% Pronase (for 30 min at 37°C). Slides were washed in 0.05 mol/L Tris-NaCl buffer (pH 7.6) and then incubated in 20% FCS for 10 min. For ER, slides were incubated for 15 min with an avidin-biotin blocking kit (Vector SP2001).

Primary antibodies were added for 1 to 2 h. The following antibodies were used: for ER, 1D5 (1:50 dilution, DAKO); for HER2, CB-11 (1:40 dilution, Novocastra); for IGFBP5, Ab4255 (1:200, Abcam); for TFF1, B110.1 (Abcam 8761, 1:10, Abcam) for vimentin, Ab7783 (1:300, Abcam).

After primary antibody incubation, sections were washed in Tris-NaCl buffer. A streptavidin-biotin multilink method (StrAviGen Multilink kit; Biogenex) was used for detection of reactivity. Sections were stained with secondary multilink antibody (1:20 dilution for 30 min), followed by horseradish-peroxidase–labeled streptavidin complex (1:20 dilution for 30 min). Diaminobenzidine tetrachloride was used as chromogen and applied for 5 min. For sections stained for ER, the DAKO EnVision-HRP visualization system was used according to the manufacturer's instructions. Sections were lightly counterstained in hematoxylin, dehydrated, and mounted.

Expression was measured by a scoring system consisting of the product of the percentage of positively stained tumor cells and intensity of staining (0-3) producing a histoscore ranging from 0 to 300.

Statistical considerations. The primary end point of this study was the overall response rate (ORR). Using Rustin's criteria, the previous phase II study done in Edinburgh reported an 8% ORR in unselected patients and a 25% CA125 response rate in the "potentially endocrine-sensitive" group (11). In view of this, a standard two-stage trial was

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Table 1. Patient and treatment characteristics

Characteristic	Number of patients (%)
Total	44 (100)
Histology	
Serous	23 (52)
Endometrioid	4 (9)
Mixed/other	17 (39)
Differentiation	
Well differentiated	2 (5)
Moderately differentiated	7 (16)
Poorly differentiated	31 (70)
Not known	4 (9)
Years from initial diagnosis	
<2	19 (43)
2-5	21 (48)
>5	3 (7)
Not known	1 (2)
Number of lines of previous chemotherapy	
1	23 (52)
2	10 (23)
>2	10 (23)
Not known	1 (2)
Platinum sensitivity	
Platinum resistant	19 (43)
Platinum sensitive	23 (52)
Not known	2 (5)

unlikely to be informative because it was improbable that the stopping rule (i.e., to terminate only if no responses are observed in the first stage) would be required. Therefore, a single stage design was used to estimate the response rate. The entry of 33 evaluable "endocrine-sensitive" patients in the phase II extension study ensured a power of 80% to conclude that the response rate was significantly higher than 10%.

Results

Patient characteristics. A total of 44 patients were recruited to the study. The median patient age was 62 years (range, 39-81 years; see Table 1). Two patients with less than two follow-up CA125 values and no follow-up CT scan were considered to be nonevaluable as defined by the protocol. The remaining 42 patients were evaluable by either CA125 or RECIST criteria, but only 33 by radiological response.

Antitumor activity. Of 42 patients evaluable for CA125 response, 7 (17%) responded according to CA125 criteria (decrease of >50%). Eleven (26%) patients had not progressed (doubling of CA125) following 6 months on treatment. Seven (17%) of the patients received treatment for <12 weeks. This latter group was considered to have progressed on treatment because withdrawal from the study was for reasons such as clinical or radiological progression, need for drainage of ascites, or symptomatic deterioration, although in some cases, letrozole therapy was administered for as little as 5 weeks. In the CA125 responders, the nadir CA125 ranged from 0.7% to 49% of baseline (actual % of baseline: 0.7, 2.6, 11.1, 17.6, 23.6, 42.6, and 49.0). The time taken to achieve the nadir CA125 value in CA125 responders ranged from 10 to 36 weeks, with a median of 13 weeks. The pattern of CA125 response is shown in Fig. 1.

Of the 33 patients evaluable for radiological response, 3 (9%) had a PR, one of which was unconfirmed, and 14 (42%) had stable disease at 12 weeks. One of the patients who responded radiologically remains stable clinically and radiologically after 17 months on treatment. Interestingly, her CA125 only remained stable throughout. The overall best response (CT or CA125 criteria) is 19%. The efficacy data are summarized in Table 2.

Of particular note, five of the seven CA125 responders had ER immunoscores between 250 and 300, whereas the other two had immunoscores of 200 to 250, suggesting that response was more likely in cancers with the highest level of ER expression ($P = 0.028$; χ^2 test for trend). In the subgroup of patients with the highest ER immunoscores (250-300), the CA125 response rate was 33%. By RECIST criteria, 17% of this group showed a PR, and 67% showed disease stabilization.

There was no significant association between response to letrozole and number of previous lines of chemotherapy,

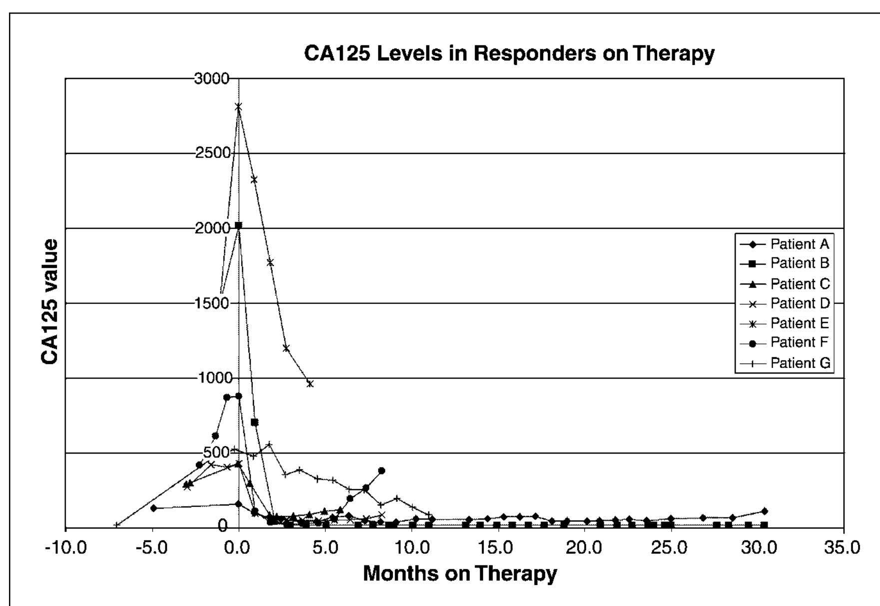

Fig. 1. CA125 levels measured in CA125 responders on treatment.

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Table 2. Efficacy data in 42 patients

Type of response	Number of patients (%)
CA125	
Response	7 (17)
Less than twice baseline at 6 mo	11 (26)
RECIST	
Partial response	3 (9)
Stable disease at 12 wks	14 (42)
Overall best response	8 (19)
Progression-free survival	
>6 mo	11 (26)
≥2 y	2 (5)

platinum resistance, tumor stage, grade, or histology, but this is not surprising because the majority of patients were all stage III grade 3 tumors (see Table 3).

Overall, 11 patients (26%) had a PFS of >6 months, and 2 patients (5%) had a PFS of ≥2 years.

Safety. Toxicity from letrozole in this patient group was minimal. No patients required to stop letrozole because of toxicity. A total of 18 patients (41%) described no toxicity at all. The main toxicities encountered were hot flushes (15 patients), myalgia/arthralgia (10 patients), headache (9 patients), nausea (7 patients) and fatigue (7 patients).

Predictive markers associated with response to letrozole. For predictive marker analysis, patients whose CA125 level decreased or increased by <50% at 12 weeks were compared with patients whose CA125 level increased by >50% at 12 weeks, as in our previous study (11).

When HER2 expression was compared in patients demonstrating either a CA125 response or <50% increase in CA125 level at 12 weeks, a similar association was again identified with high HER2 being associated with CA125 progression (Fig. 2A).

We next explored several markers, namely, TFF1, IGFBP-5, and vimentin, that we had recently identified as being regulated by estrogen in an estrogen-growth–responsive ER-positive ovarian cancer cell line (9). The first is up-regulated by estrogen *in vitro*, whereas the latter two are down-regulated. Consistent with this pattern, the mean expression value of TFF1 was higher in tumors from patients where there was a CA125 decrease or a CA125 increase of <50% as opposed to a CA125 increase of >50% (Fig. 2B). Conversely, mean expression values for both IGFBP5 and vimentin were lower in tumor sections from patients in the former group (Fig. 2C and D).

Discussion

We have previously shown *in vitro* and *in vivo* evidence that the proliferation of ER-positive ovarian cancer cell lines is stimulated by estrogen, and that this effect can be blocked by anti-estrogens such as tamoxifen (5, 6, 14). This effect was not seen in ER-negative ovarian cancer cell lines (5, 7). A number of studies have investigated the role of hormonal agents in the treatment of epithelial ovarian cancer (EOC). The response to single agent tamoxifen has been evaluated in heterogeneous settings in several small studies (4, 15–22), and the results achieved were predictably variable. A Cochrane Database Systematic Review of tamoxifen for relapse of ovarian cancer reported a 10% objective response rate and a 32% disease stabilization rate (23).

Three previous phase II studies have investigated the role of aromatase inhibitors in relapsed EOC. Del Carmen et al. (24) treated 53 patients with recurrent/persistent mullerian cancer with anastrazole. Of the 29 patients with measurable disease, one had a partial response by WHO criteria, but disease stabilization of >90 days was reported in 42% of 53 evaluable patients (radiological or CA125 criteria). Their only responder had ER-positive cancer, but no statistically significant association between ER status and response to anastrazole was shown. In a study of letrozole in 27 patients with relapsed or recurrent EOC, Papadimitriou et al. (25) showed a response in 3 out of 21 patients with measurable disease (ORR = 15%). Using criteria for CA125 response, a marker response was shown in 4 out of 27 CA125 evaluable patients (15%) with marker stabilization in a further five patients (18%). Again, although all three patients responding by WHO criteria expressed ER, no significant correlation between response and ER status was identified. In our previous study of letrozole in unselected patients with relapsed EOC, we identified an endocrine-sensitive subgroup with an ER histoscore of >150. That study showed a statistically significant association between ER status and response to letrozole, which was not observed in the other two studies of aromatase inhibitors in this setting. This may be due to differences in technique of ER estimation, size of study, or prior exposure to hormonal agents (allowed in the study of Papadimitriou et al.). The aim of the present study was, for the first time, to use ERα expression to direct treatment in ovarian cancer and confirm the efficacy of letrozole in this subset of EOC patients.

The CA125 response rate increased from 9% in the initial trial of unselected patients to 17% in the present study and

Table 3. Association of CA125 response with other parameters

Parameter	CA125 response	CA125 nonprogressor	CA125 progressor
ER			
250-300	5	4	4
200-249	2	7	5
150-199	0	5	4
Histology			
Serous	3	10	8
Endometrioid	1	1	1
Clear cell	1	0	1
Mucinous	0	1	0
Adenocarcinoma	1	1	1
Mixed/other	1	3	2
Grade			
Poor	4	13	9
Moderate	2	2	2
Well	0	1	1
Not known	1	0	1

NOTE: Six patients were nonevaluable for CA125 analysis on the basis that their CA125 values had not doubled but had progressed by RECIST criteria and discontinued treatment.

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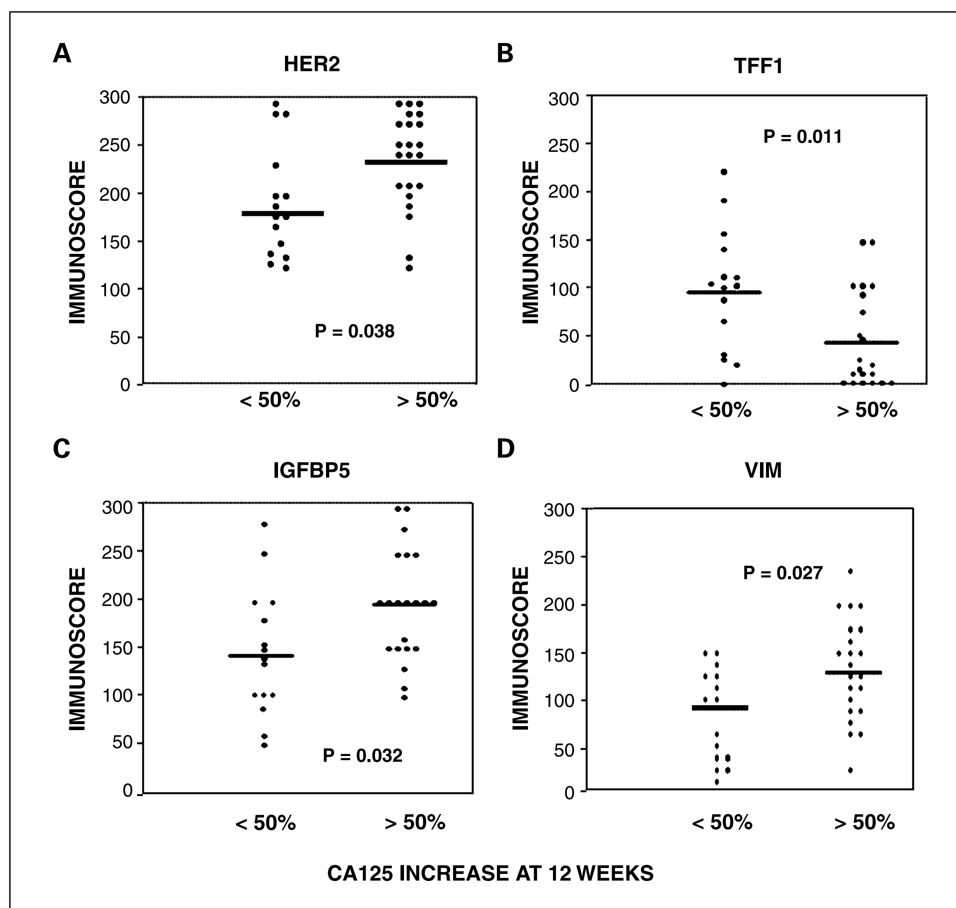

Fig. 2. Expression of HER2, TFF1, IGFBP5, and vimentin in primary tumors and association with CA125 response after treatment at 12 wks. Sections were obtained from primary tumors and stained with specific antibodies as described in Materials and Methods. Immunoscores for individual tumors are shown; *bars,* mean values for the group. Differences between the groups were assessed by Student's *t* test. *A,* HER2. Mean immunoscore values were 189 versus 230 (P = 0.038); *B,* TFF1. Mean immunoscores were 97 versus 45 (P = 0.011); *C,* IGFBP5. Mean immunoscores were 144 versus 192 (P = 0.032); *D,* vimentin. Mean immunoscores were 90 versus 129 (P = 0.027).

the CA125 stabilization rate at 12 weeks from 25% to 36%, indicating that selecting on the basis of ER expression increased the likelihood of response. This mirrors observations in breast cancer where the highest response rates are achieved in tumors with the highest ER expression (26, 27). Furthermore, we showed associations between the expression of a number of estrogen-regulated markers and outcome. This provides further support for the concept that many ER-positive ovarian cancers are estrogen regulated and indicates that the growth response might be linked to a molecular signature.

Consistent with estrogen-regulated transcription, TFF1 protein expression was higher, and HER2, IGFBP5, and vimentin expression were lower in letrozole-sensitive tumors. TFF1 is a well-defined estrogen-regulated gene and is strongly induced by E_2 in ER-positive breast cancer cells (28, 29). In contrast, HER2 has been shown to be transcriptionally repressed by E_2 (30, 31). IGFBP5 is also down-regulated by estrogen and up-regulated by the pure anti-estrogen fulvestrant (faslodex, ICI 182,780), and because a targeted antisense to IGFBP5 can inhibit the growth effects of estrogen and anti-estrogens, it has been proposed to play a role in the modulation of proliferation (32). Vimentin expression is frequently inversely associated with ER expression in breast cancers (33, 34), and we had found it to be 3-fold down-regulated by E_2 in our ovarian cancer model (35). These proteins require further testing in a prospective cohort of patients but could potentially be used to predict letrozole sensitivity. Statistically, we found cross-correlation between IGFBP5 and TFF1 (P = 0.012), IGFBP5 and vimentin (P = 0.035), and HER2 and vimentin (P = 0.008).

The aim of this study was not to show that letrozole was superior to other hormonal agents in the treatment of ovarian cancer, but that preselection of patients according to ER status results in a significant percentage of patients benefiting from anti-estrogen therapy. Unlike tamoxifen, letrozole is a pure anti-estrogen. The response rate observed in this population of patients, 46% of whom had received ≥2 preceding lines of chemotherapy and 43% of whom had platinum-resistant disease, approaches that observed with salvage chemotherapy in this setting. However, in view of the fact that the time to CA125 nadir in responders was 10 to 36 weeks and that a significant proportion of patients in this study (17%) received <12 weeks of therapy, we believe that the optimal use of letrozole in ovarian cancer is earlier in the disease course, for example, immediately following first-line chemotherapy in a role analogous to that of adjuvant hormone therapy in breast cancer. The excellent toxicity profile of letrozole also favors this role. This hypothesis requires testing in a phase III trial.

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References

1. Greenlee RT, Hill-Harmon MB, Murray T, et al. Cancer statistics, 2001. CA Cancer J Clin 2001;51:15–36.
2. McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med 1996;334:1–6.
3. Piccart MJ, Bertelsen K, James K, et al. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. J Natl Cancer Inst 2000;92:699–708.
4. Hatch KD, Beecham JB, Blessing JA, et al. Responsiveness of patients with advanced ovarian cancer to tamoxifen. Cancer 1991;68:269–71.
5. Langdon SP, Hawkes MM, Lawrie SS, et al. Oestrogen receptor expression and the effects of estrogen and tamoxifen on the growth of human ovarian carcinoma cell lines. Br J Cancer 1990;62:213–6.
6. Langdon SP, Ritchie A, Young K, et al. Contrasting effects of 17β-estradiol on the growth of human ovarian carcinoma cells *in vitro* and *in vivo*. Int J Cancer 1993;55:459–64.
7. Langdon SP, Hirst GL, Miller EP, et al. The regulation of growth and protein expression by estrogen *in vitro*: a study of 8 human ovarian carcinoma cell lines. J Steroid Biochem Mol Biol 1994;50:131–5.
8. Langdon SP, Rabiasz GJ, Hirst GL, et al. Expression of the heat shock protein HSP27 in human ovarian cancer. Clin Cancer Res 1995;1:1603–9.
9. Walker G, Langdon SP, MacLeod K, et al. Identification of estrogen-regulated biomarkers in ovarian cancer patients treated with letrozole, American Association for Cancer Research Annual Conference. Proc Amer Assoc Cancer Res 2006;47:2323.
10. Dowsett M, Jones A, Johnston SR, et al. *In vivo* measurement of aromatase inhibition by letrozole (CGS 20267) in postmenopausal patients with breast cancer. Clin Cancer Res 1995;1:1511–5.
11. Bowman A, Gabra H, Langdon SP, et al. CA125 response is associated with estrogen receptor expression in a phase II trial of letrozole in ovarian cancer: identification of an endocrine-sensitive subgroup. Clin Cancer Res 2002;8:2233–9.
12. Rustin GJ, Nelstrop AE, Tuxen MK, et al. Defining progression of ovarian carcinoma during follow-up according to CA 125: a North Thames Ovary Group Study. Ann Oncol 1996;7:361–4.
13. Rustin GJ, Marples M, Nelstrop AE, et al. Use of CA-125 to define progression of ovarian cancer in patients with persistently elevated levels. J Clin Oncol 2001;19:4054–7.
14. Langdon SP, Crew AJ, Ritchie AA, et al. Growth inhibition of oestrogen receptor-positive human ovarian carcinoma by anti-oestrogens *in vitro* and in a xenograft model. Eur J Cancer 1994;30A:682–6.
15. Markman M, Webster K, Zanotti K, et al. Phase 2 trial of carboplatin plus tamoxifen in platinum-resistant ovarian cancer and primary carcinoma of the peritoneum. Gynecol Oncol 2004;94:404–8.
16. Benedetti Panici P, Greggi S, Amoroso M, et al. A combination of platinum and tamoxifen in advanced ovarian cancer failing platinum-based chemotherapy: results of a phase II study. Int J Gynecol Cancer 2001; 11:438–44.
17. Markman M, Webster K, Zanotti K, et al. Use of tamoxifen in asymptomatic patients with recurrent small-volume ovarian cancer. Gynecol Oncol 2004; 93:390–3.
18. Van Der Velden J, Gitsch G, Wain GV, et al. Tamoxifen in patients with advanced epithelial ovarian cancer. Int J Gynecol Cancer 1995;5:301–5.
19. Markman M, Iseminger KA, Hatch KD, et al. Tamoxifen in platinum-refractory ovarian cancer: a Gynecologic Oncology Group ancillary report. Gynecol Oncol 1996;62:4–6.
20. Slevin ML, Harvey VJ, Osborne RJ, et al. A phase II study of tamoxifen in ovarian cancer. Eur J Cancer Clin Oncol 1986;22:309–12.
21. Shirey DR, Kavanagh JJ, Jr., Gershenson DM, et al. Tamoxifen therapy of epithelial ovarian cancer. Obstet Gynecol 1985;66:575–8.
22. Schwartz PE, Keating G, MacLusky N, et al. Tamoxifen therapy for advanced ovarian cancer. Obstet Gynecol 1982;59:583–8.
23. Williams CJ. Tamoxifen for relapse of ovarian cancer. Cochrane Database Syst Rev:CD001034, 2001.
24. del Carmen MG, Fuller AF, Matulonis U, et al. Phase II trial of anastrozole in women with asymptomatic mullerian cancer. Gynecol Oncol 2003;91:596–602.
25. Papadimitriou CA, Markaki S, Siapkaras J, et al. Hormonal therapy with letrozole for relapsed epithelial ovarian cancer. Long-term results of a phase II study. Oncology 2004;66:112–7.
26. Dixon JM, Jackson J, Renshaw L, et al. Neoadjuvant tamoxifen and aromatase inhibitors: comparisons and clinical outcomes. J Steroid Biochem Mol Biol 2003;86:295–9.
27. Hawkins RA. How best to express oestrogen receptor active. Eur J Cancer 2000;4:S21–3.
28. Masiakowski P, Breathnack R, Bloch J, et al. Cloning of cDNA sequences of hormone-regulated genes from the MCF-7 human breast cancer cell line. Nucleic Acid Res 1982;10:7895–903.
29. Jakowlew S, Breathnack R, Jeltsch J-M, et al. Sequence of the pS2 mRNA induced by estrogen in the human breast cancer cell line MCF-7. Nucleic Acid Res 1984;12:2861–77.
30. Dati C, Antoniotti S, Taverna D, et al. Inhibition of c-erbB-2 oncogene expression by estrogens in human breast cancer cells. Oncogene 1990;5:1001–6.
31. Bates NP, Hurst HC. An intron 1 enhancer element mediates oestrogen-induced suppression of ERBB2 expression. Oncogene 1997;15:473–81.
32. Huynh H, Yang X, Pollak M. A role for insulin-like growth factor binding protein 5 in the anti-proliferative action of the antioestrogen ICI 182780. Cell Growth Differ 1996;7:1501–6.
33. Cattoretti G, Andreola S, Clemente C, et al. Vimentin and p53 expression on epidermal growth factor receptor-positive, oestrogen receptor-negative breast carcinomas. Br J Cancer 1988;57:353–7.
34. Domagala W, Lasota J, Bartkowiak J, et al. Vimentin is preferentially expressed in human breast carcinomas with low estrogen receptor and high Ki-67 growth fraction. Am J Pathol 1990;136:219–27.
35. O'Donnell AJ, Macleod KG, Burns DJ, et al. Estrogen receptor-α mediates gene expression changes and growth response in ovarian cancer cells exposed to estrogen. Endocr Relat Cancer 2005;12:851–66.

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