

# The Role of Hormonal Therapy in Gynecological Cancers—Current Status and Future Directions

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**Abstract:** Many gynecological cancers, including epithelial and stromal ovarian cancers; endometrial carcinomas; and some gynecological sarcomas, in particular endometrial stromal sarcomas, express estrogen and/ or progesterone receptors. Hormonal therapy, typically progestogens or tamoxifen, is commonly prescribed to patients with potentially hormone-sensitive recurrent or metastatic gynecological cancers with very variable response rates and clinical benefit reported. Aromatase inhibitors are now widely used to treat postmenopausal women with hormone receptor-positive breast cancers as they have greater activity than tamoxifen and are generally better tolerated. The role of aromatase inhibitors in gynecological cancers is uncertain and has not been well studied, although they do appear to be active. The current evidence to support the use of hormonal therapies including aromatase inhibitors in gynecological cancers is reviewed, and the gaps in our knowledge highlighted.

**Key Words:** Aromatase inhibitors, Gynecological neoplasms, Ovarian neoplasms, Endometrial neoplasms, Hormonal therapy

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Many gynecological cancers, including epithelial and stromal ovarian cancers; endometrial carcinomas; and some gynecological sarcomas, in particular endometrial stro-

mal sarcomas (ESSs), express estrogen (ER) and/or progesterone (PR) receptors.<sup>1–4</sup> There are numerous case reports, retrospective studies, and small phase 2 studies, using a variety of hormonal therapies in patients with recurrent/metastatic gynecological cancers. The most commonly used agents include particular progestogens,<sup>5</sup> tamoxifen,<sup>6,7</sup> and luteinizing hormone-releasing hormone (LHRH) agonists.<sup>8,9</sup> More recently, aromatase inhibitors<sup>10,11</sup> have also been prescribed. There is evidence of tumor response and clinical benefit with all of these agents in gynecological cancers, but the degree of activity and the response rates have varied considerably.<sup>12</sup> This variability almost certainly reflects the heterogeneous populations treated with some studies and reports including patients with hormone receptor-negative tumors and high-grade cancers as well as women with chemotherapy-resistant tumors with a poor performance status where response rates are generally very low. Although there are data to suggest that women with well-differentiated and/or hormone receptor-positive tumors are more likely to benefit from hormonal therapy, there are conflicting findings regarding the predictors of response in the literature, and very few prospective studies have been performed.

Hormonal therapy is in many ways more attractive than chemotherapy for treatment of women with recurrent/metastatic gynecological cancers, where the objective of

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treatment is palliation and prolongation of survival rather than cure. Hormonal therapy is generally better tolerated and, in contrast to chemotherapy, can be administered for prolonged periods with relatively little cumulative toxicity.

Tamoxifen is commonly prescribed to women with recurrent ovarian cancers, particularly in asymptomatic women with a rising CA125 as well as in patients with chemotherapy-resistant disease,<sup>6,7,13</sup> whereas progestogens have been widely used in women with metastatic or recurrent well-differentiated endometrial cancers as well as in patients with ESSs.<sup>12,14</sup> Reported response rates are variable and difficult to interpret, as only a small number of patients have been treated on clinical trials, and most studies have been on unselected populations. There is good evidence that aromatase inhibitors are more active than tamoxifen in women with hormone receptor-positive breast cancer,<sup>15</sup> and there is growing interest in evaluating these agents in women with potentially hormone-responsive gynecological cancers.<sup>16,17</sup> The current level of published evidence is limited to small phase 2 studies in women with recurrent endometrial cancer and ovarian cancer,<sup>11</sup> as well as anecdotal reports of response to aromatase inhibitors in women with endometrial carcinomas,<sup>18</sup> ESSs,<sup>19</sup> and granulosa cell tumors.<sup>20</sup> Many of these reports have not selected patients on the basis of tumor hormone receptor status, and this will almost certainly have influenced response and clinical benefit to hormonal therapy. Prospective studies are required to determine the activity and role of aromatase inhibitors in patients with potentially hormone-responsive gynecological cancers.

## OVARIAN CANCER

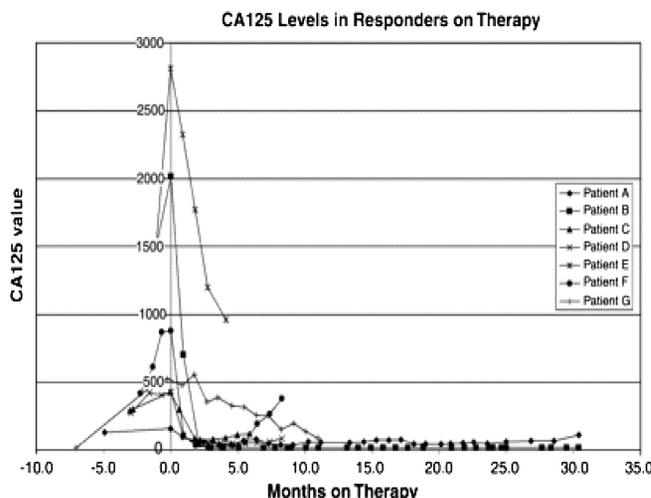
A significant percentage of ovarian cancers express both ER and/or PR receptors. There is considerable variability in the reported frequency of ER and PR expression in ovarian cancer ranging from 6% to 77% for ER and 26% to 43% for PR,<sup>6,7,11,13,16,17,21</sup> not least because of differences in scoring immunohistochemistry slides and defining cutoffs. However, a recent study in a large number of ovarian cancers reported that 36% were ER positive and 20% PR positive, and this is probably the most reliable study given its size and methodology.<sup>22</sup> This study also found a significant variability between various histological subtypes, with 43% of serous ovarian cancers being both ER and PR positive, but only 16% of borderline serous ovarian tumors were ER positive and 20% were PR positive.<sup>22</sup>

A Cochrane Database systematic review of tamoxifen in unselected women with recurrent ovarian cancer reported a 10% objective response and a 32% disease stabilization rate.<sup>6</sup> The patients treated were very heterogeneous and included asymptomatic patients with a rising CA125, as well as symptomatic patients with chemotherapy-resistant disease who had been heavily pretreated and had a poor performance status. A Gynecologic Oncology Group (GOG) study reported a 13% objective response rate with tamoxifen in patients with platinum refractory disease with a median response duration of 4.4 months, which is not dissimilar to chemotherapy in this population of patients.<sup>13</sup> Tamoxifen is commonly used in the community to treat asymptomatic

patients with a rising CA125, an approach supported by retrospective studies that have suggested that tamoxifen may delay subsequent administration of chemotherapy for symptomatic progression in this patient population<sup>7</sup> and currently being tested prospectively in a UK study by using rate of CA125 change.<sup>23</sup> In 1 study, 42% of patients remained on tamoxifen for more than 6 months, and 19% for more than 12 months; however, these patients were unselected, and there were no data on ER/PR status of the tumors.<sup>6</sup>

There have been a small number of phase 2 trials of aromatase inhibitors in ovarian cancer.<sup>11,16,21,24</sup> Bowman et al<sup>16</sup> initially reported the results of a phase 2 trial in an unselected group of patients with recurrent ovarian cancer. Of the 60 patients recruited, 50 were evaluable by Union for International Cancer Control criteria; 10 patients had stable disease for at least 12 weeks, and although no complete or partial responses were seen, a CA125 response was observed in 5 patients, and CA125 was stable in an additional 14 patients. Tumors from the Union for International Cancer Control stable disease group had significantly higher ER and PR values compared with the group of patients who progressed on treatment.

These results led the same group to carry out a similar phase 2 study of letrozole in an enriched population of patients with potentially hormone-responsive ovarian cancer with ER tumors.<sup>21</sup> The study recruited 42 women with ER-positive recurrent ovarian cancer with Gynecologic Cancer Intergroup evidence of CA125 progression. Forty-six percent had received more than 2 lines of treatment, and 43% had platinum-resistant disease. There was a CA125 response documented in 17% of women, and 26% had stable disease after 6 months of treatment (Fig. 1). Of 33 patients evaluable for objective response, 9% had a partial response. Subgroup analysis confirmed higher response rates in patients with a high ER immunohistochemistry score. In this study, no CA125 responses were seen in patients whose tumors had an immunohistochemistry score of 150 to 199, whereas



**FIGURE 1.** CA125 levels measured in CA125 responders on treatment as reported by Smyth et al<sup>21</sup> (reproduced with permission).

a CA125 response was seen in 12% and 33% of patients with tumor immunohistochemistry score between 200 to 249 and 250 to 300, respectively (Fig. 2). These promising results need to be confirmed in an independent study.

There have also been other phase 2 studies of aromatase inhibitors in ovarian cancer with lower response rates, which may be due to the very different populations treated in the various studies.<sup>11,24</sup> Although most patients who had an objective response in these studies had ER-positive tumors, this was not a consistent finding in all studies, and the discrepancy could be due to the differences in techniques of measuring ER, size of the studies, the extent of prior treatment, and possibly also the effect of prior hormonal therapy.

It seems reasonable to speculate that the optimal time to consider hormonal treatment is earlier in the disease trajectory, such as in asymptomatic patients with CA125 progression and small-volume disease and who have hormone receptor-positive tumors. These patients do not benefit from early initiation of chemotherapy before symptomatic progression,<sup>25</sup> and watchful waiting and inclusion in novel trials using CA125 response or change in doubling time as end point are potential treatment strategies.<sup>26</sup> This population has not been specifically targeted in the studies to date, and most studies have included a very heterogeneous group of patients usually with advanced chemotherapy-resistant disease. However, there may also be a place for hormonal therapy in selected patients with hormone receptor-positive recurrent cancer who have more advanced disease who have had a number of lines of chemotherapy, and arguably, they represent a group of patients in whom disease control with minimal toxicity is particularly important.

There are only scattered case reports regarding hormonal therapy in women with recurrent borderline or microinvasive ovarian cancers and in women with recurrent low-grade serous cancers,<sup>9</sup> but ER and PR overexpression is relatively common among these tumor types,<sup>2,9</sup> and a

more rigorous assessment of hormonal therapy is warranted. There remains a need to determine the role of hormonal therapy, specifically aromatase inhibitors, in ovarian cancer and specifically to identify patients more likely to respond on the basis of ER and/or PR status.

## ENDOMETRIAL CANCER

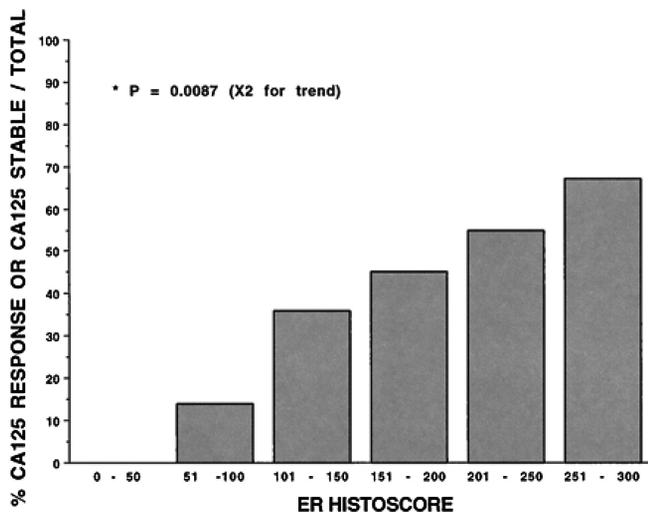
Endometrial cancer is the most prevalent gynecological cancer in the Western world. Endometrial cancers can be subdivided into type 1 (potentially hormone responsive) and type 2 (hormone independent) subtypes. Type 1 endometrial cancers are ER related and are histologically low-grade endometrioid carcinomas. Most of these tumors express either ER and/or PR receptors. These patients typically have risk factors such as obesity, diabetes, and hypertension. Even though these patients generally have a good prognosis, a small number present with metastases, and others relapse at a later time, whereas others may be unfit for surgery or radiotherapy at presentation.

A response rate of up to 70% with progestogens has been reported in women with PR-positive endometrial cancers compared with 12% in women with PR-negative tumors.<sup>5,12,27</sup> Using more rigorous response criteria in multi-institutional studies, the objective response rates are lower and range from 15% to 20%.<sup>5</sup> Features that predict a better response are hormone receptor expression, low-grade histology, and a long disease-free interval between initial diagnosis and recurrence.<sup>5,12,27</sup> In 1 GOG study, the response rates to progestogens were 37% in PR-positive and 8% in PR-negative tumors, and similar differences in response were seen in grade 1 versus grade 3 tumors.<sup>5</sup> Although progestogens have been the mainstay of hormonal treatment in women with recurrent/metastatic endometrial cancer for many years, these agents are associated with significant adverse effects, including weight gain, hypertension, fluid retention, increased blood sugar, insomnia, tremor, thrombosis, and pulmonary emboli. These can potentially worsen the quality of life and may be life threatening.<sup>5</sup>

Tamoxifen also has documented single-agent activity in 10% to 20% of women when given first line, but is much lower in the second-line setting.<sup>12</sup> The median survival of women in the GOG studies with progestogens was about 11 months, and clearly more effective hormonal therapies are needed.<sup>5</sup>

In postmenopausal women, the principal source of ER is through conversion of androstenedione by aromatase in peripheral adipose tissue. In addition to peripheral aromatization, aromatase is elevated in endometrial cancer stroma, and locally produced ER may act in a paracrine fashion to stimulate cancer growth.<sup>10,12,18</sup>

The response rates to aromatase inhibitors in recurrent and metastatic endometrial cancer have been low (10% objective response rates), but this almost certainly reflects the population who were treated.<sup>18</sup> In the studies that have been reported, most patients have had high-grade, hormone receptor-negative cancers, where a low likelihood of response would be expected. There is still a need to evaluate aromatase inhibitors in women with well-differentiated and/or hormone



**FIGURE 2.** Relationship between histochemistry score and response as reported by Bowman et al<sup>16</sup> (reproduced with permission).

receptor-positive tumors, where the expected response to treatment is likely to be higher.

### UTERINE SARCOMAS

Uterine sarcomas are uncommon malignancies that include ESSs, leiomyosarcomas (LMSs), and adenosarcomas. There have been individual case reports of response to hormonal therapy in all these subtypes; however, drawing any conclusions is impossible because of the small numbers of patients.<sup>12,19,28-30</sup> Despite the lack of prospective trials, hormone therapy has become standard of care in patients with metastatic ESS.<sup>14</sup>

A large proportion of ESS is ER positive and PR positive, and durable responses to progestogens have been reported.<sup>4,12,29</sup> Tamoxifen is contraindicated in these patients as there have been reports of stimulation of growth due to the partial ER agonist effect of tamoxifen.<sup>31</sup> Aminoglutethimide has been reported to be active, and 2 patients with lung metastases had complete responses for 14 and 7 years, respectively.<sup>29</sup> Aminoglutethimide has been superseded by third-generation aromatase inhibitors such as anastrozole and letrozole. There are few reports of response to letrozole. One study reported 8 responses from 10 patients treated.<sup>14,31</sup> Interestingly, most low-grade ESSs express aromatase. The staining pattern, however, is heterogeneous.<sup>14,28</sup> The high percentage of aromatase positivity in low-grade ESSs may have implications in the management of these tumors. Patients with measurable disease and metastatic ESS should be con-

sidered for treatment with an aromatase inhibitor. In addition, patients who are at high risk of progression, either following resection of metastases or surgical debulking, and have small-volume, nonmeasurable disease should also be considered for treatment with an aromatase inhibitor.

Although hormonal therapy has not been widely used to treat women with uterine LMSs, a study using paraffin-embedded tissue blocks from 15 cases of uterine LMS from the Cleveland Clinic Foundation suggests that hormonal treatment may have a role.<sup>1</sup> These tumors are usually chemoresistant, and there are few options for patients with metastatic disease, particularly after chemotherapy. The investigators performed immunohistochemical staining for ER and PR on tumor specimens. Nuclear staining was evaluated by 2 observers in a semiquantitative manner according to percentage of nuclei stained: 0 = no nuclear staining, 1+ = 1% to 25%, 2+ = 26% to 50%, 3+ = 51% to 75%, or 4+ = 76% to 100% of nuclei stained. The majority of uterine LMSs stained for ER (13/15, 87%), PR (12/15, 80%), or both ER and PR (12/15, 80%), with most cases showing 3+ or 4+ positive staining.<sup>1</sup> These data strongly support a study of hormonal therapy in patients with ER-/PR-positive metastatic LMS who are not suitable for aggressive chemotherapy regimens or after relapse after chemotherapy.

### GRANULOSA CELL TUMORS

Granulosa cell tumors account for about 2% to 5% of all ovarian cancers. They are usually confined to the ovary

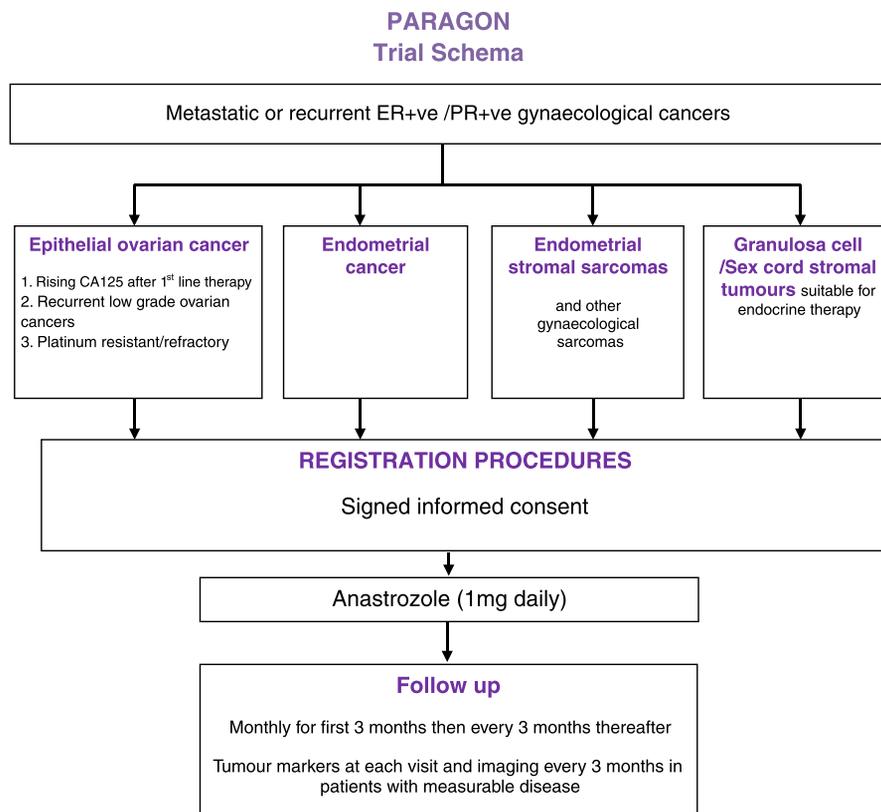


FIGURE 3. PARAGON trial schema (ACTRN12610000796088, CRUK/10/056).

and tend to have a good prognosis, but they can recur and metastasize many years after diagnosis. In 1 series from the Royal Marsden, 40% of patients with stage I disease and 60% of patients with stage II tumors had a recurrence.<sup>32</sup> They tend to be refractory to standard cytotoxic chemotherapy, leaving surgery as the mainstay of treatment. Serum inhibin levels are valuable tumor markers for the diagnosis of primary or recurrent granulosa cell tumors.<sup>33</sup>

Granulosa cell tumors are also potentially hormonally responsive, with about 30% of granulosa tumors ER positive and almost 100% PR positive. Hormonal agents such as progestogens or LHRH agonists have been used widely to treat these patients as they are often elderly and not suitable for aggressive chemotherapy.<sup>8,9,12,32,34</sup> More recently, there have been a few case reports of durable response to aromatase inhibitors in patients with metastatic granulosa cell tumors who had received multiple prior treatments.<sup>20,34</sup>

Small clinical series and case reports have described responses to LHRH agonists or progestosterones. One series of 13 patients reported a 50% response rate to LHRH agonists, whereas in 2 separate series, a total of 4 of 5 patients were reported as having responded to a progestogen.<sup>8,9</sup> Two recent case series have reported durable responses to aromatase inhibitor in a total of 6 patients.<sup>20</sup> All these patients had been intolerant of chemotherapy or experienced tumor progression despite receiving chemotherapy, and 2 of patients described had also previously received leuprolide. In all cases, there was evidence of complete or partial radiological response and sustained benefit on treatment for more than 12 months. These findings need confirmation in larger trials.

## CONCLUSIONS

Hormonal therapy is an attractive option in patients with recurrent/metastatic gynecological cancers where the objective of treatment is palliation and prolongation of survival rather than cure. Aromatase inhibitors are generally well tolerated and in contrast to chemotherapy can be administered for prolonged periods with relatively little cumulative toxicity. The degree of activity and response rates reported in previous studies have varied considerably. This variability almost certainly reflects the heterogeneous populations treated, which have included women with ER and PR receptor-negative tumors as well as those with a poor performance status where response rates are generally low. There is a clear need to investigate the role of hormonal therapies, particularly aromatase inhibitors, in selected women with potentially hormone-responsive recurrent/metastatic gynecological cancers. Prospective studies are warranted in this patient population, and future trials should focus on clinical benefit and quality of life, as well as establishing accurate response rates and identifying predictors of response. It has been very difficult to investigate the role of hormonal therapy, particularly for uncommon and rare subtypes of gynecological cancers. PARAGON (ACTRN12610000796088, CRUK/10/056) is a large prospective international study that has recently opened and will help to clarify the role of aromatase inhibitors in women with potentially hormone-responsive recurrent/metastatic gynecological tumors (Fig. 3). This study

has a unique design that increases the likelihood of successfully recruiting patients. Investigators will be able to submit a single protocol and ethics application that will encompass all eligible patients with potentially hormone-responsive recurrent/metastatic gynecological cancers, which will greatly increase recruitment and give more patients with relatively rare tumors access to clinical trials.

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