Hormone Receptors in Serous Ovarian Carcinoma: Prognosis, Pathogenesis, and Treatment Considerations

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ABSTRACT: A few breakthroughs have been accomplished for the treatment of ovarian cancer, the most deadly gynecologic carcinoma, in the current era of targeted oncologic treatment. The estrogen receptor was the first target of such treatments with the introduction of tamoxifen four decades ago in breast cancer therapeutics. Attempts to duplicate the success of hormonal therapies in ovarian cancer met with mixed results, which may be due to an inferior degree of hormone dependency in this cancer. Alternatively, this may be due to the failure to clearly identify the subsets of ovarian cancer with hormone sensitivity. This article reviews the expression of hormone receptors by ovarian cancer cells, the prognostic value of these expressions, and their predictive capacity for response to hormonal agents. The possible ways ahead are briefly discussed.

KEYWORDS: hormone receptors, estrogen receptor, progesterone receptor, ovarian cancer

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Introduction

The receptors for estrogen and progesterone hormones have a well-established prognostic and treatment-predictive role in breast cancer, but, although they have been studied in ovarian cancer, their role in that disease is less well defined. A clear benefit has not been established in several small clinical trials evaluating the role of hormone-blocking treatments in ovarian cancer, despite the fact that clinicians treating the disease often encounter positive outcomes with these treatments.[1] The reasons for this discrepancy are probably multifactorial and involve small size of the studies, poor selection of patients, and failure to use any predictive markers. Indeed, most studies usually involve only a few dozen patients, including all ovarian cancer subtypes, and some studies do not take into account the expression of the hormone receptors in tumor cells. This expression has been of paramount importance for confirming the value of hormonal treatments in breast cancer. In breast cancer, additional genomic markers are currently available to further characterize antihormone treatment sensitivity in estrogen receptor (ER)-positive cancers, and therapeutic algorithms have advanced to rely on these markers in addition to the expression of the hormone receptors.[2] Thus, success seen with hormonal therapy in breast cancer is built not only on the confirmation of the expression of the target but also on additional gene expressions. Failure to stratify patients with the aid of treatment-predictive factors may significantly impede the ability to discern the benefits of specific anticancer treatments, and this has become even more critical in the present environment of targeted treatments.

This article discusses current data on the expression of various important hormone receptors as a basis to evaluate hormone treatments for ovarian cancer in the second line or beyond setting. It will further explore ways when these treatments become optimized in the future based on predictive markers and their pathogenic implications.

ERα Expression in Ovarian Cancer and Prognostic Role

The expression of ERα receptor in ovarian carcinomas was the subject of several studies not always with concurring results (Table 1). The largest study examining ER expression was reported by the Ovarian Tumor Tissue Analysis Consortium and included 2933 ovarian cancer patients with various epithelial histologies.[3] Among these, 1742 patients had high-grade serous carcinomas. ER was positive in 81% of patients (60% strong positivity defined as ≥50% of tumor cell nuclei and 21% weak positivity defined as 1%–50% of tumor cell nuclei). In contrast to the endometrioid subtype where ER expression (both strong and weak) was a good prognostic marker, in serous carcinomas, ER was not prognostic for disease-specific survival (log-rank $P = 0.49$).[3]

Another large immunohistochemistry (IHC) study examining ER expression in 582 Danish ovarian cancer patients showed that 43% of patients were positive.[4] The definition of

Table 1. Estrogen Receptor α (ERα) expression and prognostic value in serous ovarian carcinoma.

REFERENCE	EXPRESSION % POSITIVE	IHC CUT-OFF	% HGSC	PREDICTIVE	COMMENTS
3	81%	≥50% (strong positivity) 1–50% (weak positivity)	59%	No	60% strong positivity. Confounding factors controlled for: Age, stage, grade, completeness of cytoreduction, CA125.
4	43%	≥10%	61.7%	Yes	Positivity associated with good prognosis. Confounding factors controlled for: Age, stage, grade, completeness of cytoreduction.
5	50%	mRNA expression.	–	–	10 patients with serous carcinoma. 50% positive. Controlled for the following confounding factors: Stage, grade.
6	43%	>50%	86%	Yes	95% stage II. Positivity associated with good prognosis. No multivariate analysis.
7	32%	>10%	100%	Yes	32% positive. Positivity associated with better OS and PFS. Controlled for confounding factors: Age, stage, grade, lymph node status, ERβ receptor status.
8	54%	Semiquantitative (No or weak staining versus strong staining)	100%	No	41% considered positive. Trend for good prognosis of ER positivity in younger patients. Univariate analysis negative. No multivariate analysis.
10	60.4%	>10 fmol/mg (Biochemical method)	0%	Yes	ER positivity associated with worse survival. All patients had optimally cytoreduced stage III cystadenocarcinomas. Controlled for confounding factors: Age, grade, PR status.

Abbreviations: OS, Overall Survival; PFS, Progression Free Survival; IHC, Immunohistochemistry; HGSC, High Grade Serous Carcinoma; CA125, Cancer Antigen 125.

positivity in this study was an expression of above 10%. ER positivity in the mucinous and clear cell subtype was much lower (4% and 2%, respectively) but endometrioid type had a similar ER positivity with serous carcinomas (39%). Most ER-positive serous carcinomas (30% of the total serous carcinoma patient population) had an intermediate positivity with 10%–40% of cells staining. The study also found that ER positivity across subtypes was associated with a better prognosis with a hazard ratio of 0.8 for disease-specific survival (95% confidence interval 0.63–0.99). When progesterone receptor (PR) positivity was taken additionally into account, tumors positive for both receptors had even better disease-specific survival with a hazard ratio of 0.48 (confidence interval 0.31–0.74) compared with patients negative for both receptors.[4] A small study examining ER status by mRNA expression in serous and endometrioid carcinomas confirmed 50% positivity in serous subtype and showed an even higher expression in endometrioid cancers.[5]

A study using IHC in patients who had been operated for an epithelial ovarian cancer (mostly, 86%, serous subtype) found ERα positivity at primary laparotomy, which was present in 43% of patients, to be associated with a better overall survival.[6] An IHC study of 100 serous ovarian carcinoma patients defined ERα positivity as more than 10% of cells staining positive with any intensity and found positivity in 32%.[7] ERα-positive patients had a better overall and progression-free survival than ERα-negative counterparts. A series of 148 stage III and IV serous ovarian carcinomas evaluated ER and PR expression taking into consideration the differences with the age of the patient at presentation.[8] ER positivity was higher in tumors of older patients, while the reverse was true for PR. Although no prognostic role of ER and PR was found in the entire cohort, a trend toward a better prognosis of ER- and PR-positive tumors was observed in younger patients.[8] In contrast, another study that included serous ovarian carcinomas found no association of ER protein expression (either as a continuous variable or with 30% positivity as a cutoff) for overall or relapse-free survival.[9] Additionally, this study found an adverse effect of higher ER mRNA expression in these cancers when incorporated in a predictive model together with ER target gene *EIG121*. An adverse prognostic value for ER-positive tumors was also reported in another series of 96 optimally cytoreduced serous ovarian cystadenocarcinomas.[10] This study used a biochemical assay instead of IHC with a cutoff value of 10 fmol/mg to determine ER positivity. The worse survival of ER-positive patients was due to late deaths, after three years from surgery.[10]

Different cutoff points, antibodies used, and techniques as well as different populations studied may explain the variable results in these studies. Nevertheless, most of the available data pinpoint to ERα positivity by IHC, which is present in various degrees in the majority of patients, to be a good prognostic marker in serous ovarian carcinoma (Table 1). Of interest is that the only study examining serous cystadenocarcinomas found a reverse influence of ER expression in survival. This observation argues for the importance of patient selection in therapeutic trials, given that different prognostic implications of a marker may also underline the variability in the value of treatments targeting the marker.

Alternative Estrogen Receptor Expression and Prognostic Role

Besides ERα, other estrogen receptors exist that may be of importance for treatment with estrogen-blocking agents in ovarian carcinomas, and thus, their expression may be clinically relevant. These include the alternative nuclear receptor ERβ and the membrane estrogen receptor GPER1 (G protein-coupled estrogen receptor 1, also called GPR30). The expression of ERβ at chromosome 14q23 is different from that of ERα (ERα gene is located at chromosome 6q25) and has 96% homology with ERα in their DNA-binding domain.[11] Comparatively high homology (55%) is also evident in the ligand-binding domain of the two receptors.[11] The ligand-binding pockets of the two receptors have even higher similarity and differ in only two amino acids.[12] Despite this, affinity and effect of pharmacologic ligands may differ between the two receptors due to differing structural ramifications of binding.[13]

ERβ receptor displays a high expression compared to ERα in normal ovarian epithelium, but this ratio is reversed in ovarian cancers.[14] Interestingly, similar changes in the ratio of the two ER subtypes in normal and malignant tissues have been observed in other locations such as the breast, prostate, and colon.[15] Additionally, data from a series of 42 benign and malignant ovarian tumors showed that ERβ had a higher expression in benign tumors, while ERα was higher in malignant tumors.[16] Nevertheless, not all cancer samples displayed this ERβ/ERα reversal and another study examining just a few normal ovarian surface epithelium and ovarian cancer samples found both ERα and ERβ expressed in normal tissues and a greater decrease of ERα in cancer while ERβ expression was mostly maintained.[17]

Some of the studies discussed in the previous section on ERα expression in ovarian cancer have examined the expression of ERβ in parallel. One such study that showed a good prognosis association for ERα confirmed a better prognosis in regard to overall survival also for ERβ-positive patients compared to ERβ-negative patients.[7] ERβ positivity was also associated with a lower risk for lymph node infiltration. Despite this association, ERβ was not associated with progression-free survival.[7] In a series of 43 mainly serous and FIGO III ovarian cancer patients, ERβ expression score of more than 30% was shown in 18 patients (42%) and was associated with greater chemosensitivity and a higher percentage of complete response to treatment.[18] The mRNA study discussed above in the ERα discussion also examined ERβ status in serous and endometrioid carcinomas and found a similar positivity in the two subtypes (about half of the patients positive).[5]

ERβ receptor is expressed as the full protein (called ERβ1) and as two alternatively spliced forms, namely, ERβ2 (also called ERβcx) and ERβ5.[19] Specific antibodies recognizing each of these isoforms have been developed, and their expression has been examined in ovarian cancer tissues.[20] Most cases have been confirmed to express all isoforms in a cytoplasmic, nuclear, or both locations. A cytoplasmic expression of isoform ERβ2 has been associated with a worse prognosis compared with negative cases. Nuclear localization of this isoform or expressions of the full receptor or the ERβ5 isoform have not offered prognostic information.[20] The ERβ2 isoform is a truncated protein in the carboxy-terminal part compared to ERβ1 and has decreased or absent DNA binding capacity. It acts as a negative modulator of the activity of ERα.[19] Thus, its expression may have divergent effects compared with other isoforms, and, if confirmed by additional studies, it may be of clinical value.

Human GPER1 is a completely different protein from the two estrogen nuclear receptors and mediates the effects of estrogens through signaling from the membranes of the endoplasmic reticulum.[21] Ca^{++}-mediated signals and kinase Protein kinase A (PKA) are downstream mediators of GPER1.

GPER1 was expressed in both the mRNA and protein level in approximately one-third of ovarian cancers, but no prognostic association was found.[16] In contrast, a higher percentage of ovarian cancers (80%) was reported in another series in which GPER1-positive tumors had a better disease-free survival than GPER1-negative counterparts.[22] Other investigators have pinpointed to a complex prognostic interconnection of GPER1 with the expression of the related G-coupled protein receptors for Follicle Stimulating Hormone (FSH) and Lutenizing Hormone (LH).[23] According to these data, FSH and LH receptors upregulated GPER1 but a good prognostic influence of GPER1 was evident only in ovarian tumors not expressing the two gonadotropin receptors.

Alternative ER receptors clearly deserve additional study to clarify their prognostic role in ovarian cancer, but the available data discussed above suggest that both the full ERβ protein expression and GPER1 may offer complementary to ERα prognostic information that could be exploited therapeutically.

ER Target Gene Expression and Prognostic Role

PR is the prototypic ER target gene, and in breast cancer, its prognostic role has been proposed to be due to the information it may provide regarding functional ER competence.[24] The Ovarian Tumor Tissue Analysis Consortium study showed that 31% of high-grade serous carcinomas were positive for PR (24% weak positivity and 7% strong positivity).[3] PR positivity was predictive of a better disease-specific survival (Table 2).

The previously discussed Danish study examined the expression of PR, in addition to ER, in ovarian cancer patients according to histologic subtype.[4] Positivity for PR using the same criteria used for ER was present in 19% of patients with serous carcinomas and 39% of the endometrioid type, while mucinous and clear cell carcinomas had a much lower PR positivity (6% and 4%, respectively). PR positivity conferred a better disease-specific survival with a hazard ratio of 0.69 (95% confidence interval 0.51–0.94). As previously mentioned, combined ER and PR positivity conferred an even better disease-specific survival.[4]

Table 2. Progesterone Receptor (PR) expression and prognostic value in serous ovarian carcinoma.

REFERENCE	EXPRESSION % POSITIVE	IHC CUT-OFF	% HGSC	PREDICTIVE	COMMENTS
3	31%	≥50% (strong positivity) 1–50% (weak positivity)	59%	Yes	7% strong positivity. 59% HGSC. Positivity associated with good prognosis. Controlled for the following confounding factors: Age, stage, grade, completeness of cytoreduction, CA125.
4	19%	≥10%	61.7%	Yes	61.7% HGSC. Positivity associated with good prognosis. Controlled for the following confounding factors: Age, stage, grade, completeness of cytoreduction,
25	25%	>10%	75.5%	Yes	Positivity associated with good prognosis. Controlled for confounding factors: Stage, grade, Expression of ER and AR.
8	44%	Semiquantitative (No or weak staining versus strong staining)	100%	No	55% considered positive. Higher expression of PR in younger patients. Univariate analysis negative. No multivariate analysis.
10	–	Continuous variable (Biochemical method)	0%	No	All patients had optimally cytoreduced stage III cystadenocarcinomas. Controlled for the following confounding factors: Age, grade, ER status.
27	35%	>10%	70.5%	Yes	PR-B sub-type expression associated with good prognosis. Controlled for confounding factors: Age, stage, grade, ER status.

Abbreviations: OS, Overall Survival; PFS, Progression Free Survival; IHC, Immunohistochemistry; HGSC, High Grade Serous Carcinoma, AR, Androgen Receptor.

In another IHC study, PR positivity (using a cutoff of 10%) was ~25% in serous carcinomas.[25] ER positivity in serous histology in this series was 85%. PR-positive tumors had a better prognosis and better 2-year and 5-year survival than negative cases, while ER was not prognostic.

In a series of 96 patients with stage III ovarian cystadenocarcinomas who underwent optimal cytoreduction and postoperative chemotherapy, PR status (essayed by a biochemical method instead of IHC) was not prognostic for survival.[10] Lack of prognostic value of PR expression was reported in another study of stage III and IV serous carcinomas.[8] This study also showed a higher PR expression percentage (55%) in younger ovarian cancer patients than in older ones (34%).

PR expression at the mRNA level was examined in a study of both normal and neoplastic human surface ovarian epithelium.[17] PR expression was downregulated in cancerous epitheliums compared with normal epitheliums in this investigation, and the authors suggested that this downregulation in addition to similar changes in the expression of ERα and androgen receptor (AR) may contribute to neoplastic transformation.

Similar to ER, PR subtypes exist, namely, PR-A and PR-B, but, in contrast to ER subtypes that are transcribed from different genes, they are transcribed from the same human gene with alternative splicing.[26] PR-B is the full-length receptor, while PR-A transcribed from an alternative promoter lacks the 165 amino-terminal amino acids and acts as a PR-B repressor.[26] A study that examined ER and PR subtypes in a series of 155 epithelial ovarian cancers (~70% serous) reported PR-A and PR-B as well as ERα positivity in about one-third of cases each, while ERβ was positive in 60% of cases.[27] In this study, only PR-B subtype was prognostic for survival in multivariate analysis with PR-B-positive cancers having a better prognosis than PR-B-negative counterparts.

GnRH is another target of estrogen signaling. GnRH affects ovarian cancer cells both indirectly by stimulating production of FSH and LH in the hypophysis, which then stimulate estrogen and progesterone production in the ovaries and directly as the majority of ovarian cancer cell lines and ovarian cancers express the GnRH receptor.[28–30] Four out of the six ovarian cancer cell lines and most serous carcinoma samples (15 of 16 samples examined) expressed the GnRH receptor at the mRNA level.[30] In contrast, none of the four undifferentiated and endometrioid carcinomas tested expressed the receptor. On the protein level, GnRH receptor was expressed in 70% of serous carcinomas, and its positivity was correlated with a better overall survival in a series of 139 ovarian cancer patients.[31] Estrogens regulate GnRH expression through both ER nuclear receptors and GPER1 in gonadotropin neuronal cells.[32–34] Inversely, GnRH signaling impedes ER signaling by interfering with ER dimerization, which is a prerequisite of transcriptional activity.[35] As a result, treatment of ovarian cancer with GnRH analogs or, alternatively with direct GnRH inhibitors, both currently in clinical practice for other steroid-dependent cancers,[36] could have synergistic effects with ER-directed therapies.

Evidence for Pathogenic Role of Estrogen Receptors in Ovarian Cancer from Preclinical Models

Having established the presence of hormone receptors in ovarian cancer, the next step to advance a therapeutic role involves confirmation of their involvement in pathogenesis, which implies dependence of cancer cells to their signaling. *In vitro* and *in vivo* models may inform these points.

Exposure to estrogens of several but not all ERα-positive ovarian cancer cell lines led to growth stimulation and significant upregulation or downregulation of 228 genes.[37] In contrast, estrogens had no significant effect on growth in ERα-negative or ERβ-positive cell lines in this study. In ovarian cancer cells that express ERα, transfection with ERβ had growth inhibitory effects both *in vitro* and *in vivo*, when these cells were used to form tumor xenografts in nude mice.[38] ERβ transfection of ERα-negative SKOV-3 ovarian cells resulted in slower growth and increased apoptosis after exposure to estrogens, an effect not observed when the cells were transfected with nonfunctional forms of the receptor.[39] Treatment with letrozole led to improvement of survival in a xenograft model of OVCAR-3 human ovarian carcinoma cells that are strongly positive for ER, in contrast to when an ER weakly positive cell line, DISS, was used for xenograft establishment.[40] This improvement of survival in the ER strongly positive cell line xenografted mice after letrozole treatment was associated with decreased angiogenesis and ascites production but no increase in apoptosis. In the same vein, after treatment of ovarian cancer cells expressing both ER subtypes, cell growth was suppressed by exposure to an ERα antagonist or an ERβ agonist and was promoted by exposure to an ERα agonist or an ERβ antagonist.[41] *In vivo* experiments in ovariectomized mice confirmed that xenografted mice treated with the ERα antagonist or the ERβ agonist had smaller size tumors, and the combination of the two drugs had a synergistic effect.[41] In another *in vivo* study in rats, the LH Releazing Hormone (LHRH) analog triptorelin or the aromatase inhibitor exemestane, when added to cisplatin treatment, improved the survival of the animals compared with cisplatin or hormonal therapies alone.[42]

Activation of GPER1 is also involved in signaling in ovarian cancer cells. G1 (a selective GPER1 agonist) treatment increased apoptosis and suppressed proliferation in IGROV-1 ovarian cancer cells by microtubule interruption.[43] The same treatment was confirmed to inhibit cell cycle progression and induce apoptosis in GPER1-expressing SKOV-3 and OVCAR-3 ovarian cancer cells.[22] OVCAR-3 cells displayed decreased migration when treated with estradiol, G1, or the ERα downregulator ICI182780 and tamoxifen, which are both also GPER1 agonists.[44] Thus, inhibitory effects of tamoxifen observed in ER-negative ovarian cell lines could be related to this agonistic effect on GPER1.[45] In contrast to the above results, treatment of the ERα-negative/GPER1-positive ovarian cancer cell line OVCAR5 with estradiol or G1 promoted motility and invasion in *in vitro* wound healing and transwell Matrigel assays.[46] Knockdown of GPER1 with siRNA reversed these effects. The invasion and motility promotion effect was traced in this cell line model to an upregulation of metalloproteinase MMP-9 induced by GPER1 activation.

GnRH analogs and antagonists have an inhibitory effect in human xenograft ovarian cancer cell models in nude mice.[47–49] Surgical castration of the mice in one of these studies using human BG-1 cells as xenografts resulted in the acceleration of tumor growth.[47] Both FSH and LH were elevated in the serum of ovariectomized mice compared with controls and were decreased with goserelin treatment, which also resulted in growth inhibition of BG-1 xenografts. These data argue for a direct tumor-promoting effect of GnRH or FSH and LH on ovarian tumor cells, an action that is reversed by GnRH analog treatment. Growth inhibition of human ovarian cancer cells' xenografts has also been observed after treatment with the GnRH antagonist cetrorelix in mice.[48]

GnRH receptor on the surface of human ovarian cancer cells signals through a phosphotyrosine phosphatase to downregulate receptor tyrosine kinases activity and also through JunD to inhibit cell cycle.[50] GnRH receptor signaling may have an effect in ovarian cancer peritoneal dissemination, as a study reported a decrease of dissemination after GnRH receptor downregulation through RNAi.[51] GnRH receptor downregulation resulted in the downregulation of integrins expression that normally mediates extracellular matrix adhesion.

Overall, these data pinpoint to several possible avenues to further explore the development of clinical hormonal therapies in ovarian cancer, guided by the effects seen in ovarian cancer preclinical models.

Clinical Studies of Hormone Receptors in Ovarian Cancer

A number of studies have examined the role of hormonal therapies in ovarian cancer and have been reviewed.[52–57] Thus, only selected studies that illustrate the most clinically important concepts and candidate strategies as well as newer data will be discussed here. The focus will also be on studies that include receptors expression and published in full.

Most experience exists with tamoxifen and aromatase inhibitors, while only a few studies examined fulvestrant or GnRH analogs. All studies are small phase II or retrospective series, include, at best, a few dozen patients with pretreated ovarian cancer and tend to encompass all epithelial histologies. Several have not examined receptor expression as an inclusion criterion, and some have been published only in abstract form but not in full. From these studies, some clinically useful evidence can be extracted. Treatment with tamoxifen produces a low percentage of responses in the range of 10%,[54] and only rare complete responses have been reported.[58] A much higher percentage of patients may have stabilization of their disease but usually for a brief time period, in the range of a few months. Interestingly, one series that included an induction phase with a higher dose of tamoxifen at 80 mg per day for a month before reduction to a maintenance dose of 20 mg per day showed a clinical benefit rate of 79%.[59]

Most reports on aromatase inhibitors use letrozole. In an open-labeled nonrandomized study of 60 relapsed ovarian cancer patients, letrozole 2.5 mg daily produced stabilization of the disease for at least 12 weeks in 20% of patients.[60]

Patients with ER- and PR-positive tumors had higher probabilities of stability with letrozole. Another phase II study that included only ER-positive, chemotherapy resistant, mostly serous ovarian cancer patients confirmed a partial response in one patient (3%) and stable disease in an additional 23% treated with letrozole.[61] In a study of ER-positive patients, 23 patients with serous carcinomas were included and evaluated for CA125 response.[62] From 21 evaluable patients, 62% had a response or stability of the tumor marker. Patients with higher ER expression had a higher response compared with those with intermediate expression. In a smaller study that included 15 patients with serous histology, a clinical response or stability was observed in 33% of patients and was not associated with ER expression.[63]

A recent retrospective analysis of 99 heavily pretreated (mean of four lines of prior chemotherapies) ovarian cancer patients (80% serous histology) who received either tamoxifen or aromatase inhibitors (anastrozole or letrozole) disclosed a median progression-free interval of four months.[64] Patients positive for the ER tended to have a longer progression-free interval, although this did not reach statistical significance. The same was true for aromatase inhibitors versus tamoxifen.[64]

The ER downregulator fulvestrant was evaluated in a phase II trial of ovarian cancer patients who had received multiple previous chemotherapies.[65] Fulvestrant produced stable disease by RECIST criteria in half the patients, and the mean time to disease progression was approximately two months. Decrease or stability of CA125 marker was observed in 43% of patients. Based on these results and given the advanced disease status of these patients and lack of other treatment options, fulvestrant may represent a useful and well-tolerated drug, if this study is replicated.

An interesting case report of a 53-year-old woman with ER- and PR-positive heavily pretreated with chemotherapy serous ovarian carcinoma illustrates the concept of using multiple lines of hormonal treatment.[66] The patient had an initial response to tamoxifen and subsequently to anastrozole and fulvestrant lasting for a total of 28-month chemotherapy-free interval.

PR-targeting agents have also been studied in small phase II studies in ovarian cancer. Medroxyprogesterone is a progestin with androgenic activity in addition to progestogen activity, which has been used clinically as a contraceptive. Studies have suggested that women using medroxyprogesterone contraceptives may have a decreased incidence of epithelial ovarian cancer.[67] A phase II study of chemotherapy pretreated ovarian cancer patients included 41 evaluable patients and showed one partial response and seven additional patients with disease stabilization for a clinical benefit rate of 20%.[68] In another study that included 24 chemotherapy pretreated patients, medroxyprogesterone produced one partial response, and nine patients had stable disease for a clinical benefit rate of 42%[69] although other studies showed somewhat lower rates.[70] Two other progestins, megestrol and mifepristone, have obtained a similar clinical benefit of 20%–40% in some studies,[59,71] but showed inferior efficacy in others.[72,73]

LHRH analogs' experience in ovarian cancer is also limited to small phase II studies. A phase II study that included 74 epithelial ovarian cancer patients of various histologies (only 19 with serous carcinomas) showed a 16% rate of stable disease with triptorelin.[74] Mean duration of disease stability was five months. Patients in this study were all pretreated with chemotherapy, and most had two or three lines of treatment.[74] A smaller phase II study of patients with similar characteristics showed stability of disease in eight patients (58%) for a median of 3.5 months and absence of complete or partial responses.[75] Interestingly, a complete response lasting more than 9 months has been reported with triptorelin.[76] None of these studies checked for expression of receptors as a biomarker of response.

A phase II study of 26 chemotherapy pretreated ovarian cancer patients examined the combination of monthly goserelin with tamoxifen.[77] Responses or stability for at least six months was observed in about half of the patients, and four patients were stable for at least two years. All patients had a good serum FSH and LH suppression to less than 4% of their pretreatment levels but no correlation of the level of suppression to response could be discerned.[77] ER expression on the tumors was not examined.

Another therapeutic concept takes an advantage of the expression of various receptors by tumor cells to target chemotherapeutic cytotoxic drugs to these cells by using ligands of the receptors conjugated to cytotoxic chemotherapeutics. One such compound conjugates the GnRH agonist zoptarelin with doxorubicin. This drug was examined in a phase II trial of 42 platinum refractory or resistant ovarian cancer patients with mostly serous histology.[78] A partial response was obtained in 14.3% of patients, and additionally, 35.7% of patients had stable disease. The median OS was 53 weeks, and the toxicity profile was acceptable with a few grade 3 and 4 toxicities. The authors conclude that the conjugate is a candidate for further development.

A recently reported randomized trial of 150 patients with ovarian cancer studied adjuvant hormone replacement therapy for a planned five years in women diagnosed with epithelial ovarian cancers within the previous nine months.[79] Women across stages and histologies were included and ~40% had serous histology. Fifty-three of the 72 patients who received therapy in the treatment arm had an estrogen-alone preparation, while 19 patients received estrogens combined with norgestrel. Concomitant treatments were not reported, but the median hormone therapy duration in the treatment arm was 1.14 years, suggesting that the patients may have been receiving concomitant chemotherapy during a significant part of the hormone treatment. The study showed a better overall and relapse-free survival in the replacement group.[79] There were less ovarian cancer and nonovarian cancer deaths in the hormone replacement group. As a result of the variability of

stage, histologies, and replacement treatment, as well as the unknown variable of concomitant treatments, the study is minimally helpful in informing the question of the value of hormone replacement as a therapeutic manipulation in ovarian cancer and serous histology in particular. At this point, hormone replacement could be considered for menopause symptom relief in early stage disease if no other hormone manipulation as an anticancer therapy is planned.

Perspectives

Effective treatments are needed for patients with ovarian cancer, especially in the second line and beyond, as well as the platinum refractory setting. Significant progress has been made in cancer therapeutics over the past several years with the introduction of targeted therapies that take advantage of the improved understanding of cancer biology. This unfortunately has not been the case in ovarian cancer where the only targeted treatment currently shown to produce a benefit is the Vascular Endothelial Growth Factor (VEGF) monoclonal antibody bevacizumab in the platinum-resistant recurrent setting.[80] ER is the prototypic target of cancer-targeted treatments as tamoxifen introduced several decades ago was the first antineoplastic-targeted therapy for breast cancer. Ovarian cancer arising also in an endocrine organ could be another target of this type of treatment. Experience gained from breast cancer, where hormone treatments comprise the backbone of systemic therapy for ER-positive carcinomas, and also from endometrial carcinomas, where similar hormonal treatments have been used in the second-line metastatic setting,[81] could direct further development of these treatments in ovarian cancer. Evaluation of ER expression has been instrumental in guiding ER-directed treatments in breast cancer and should be taken into consideration for further development of these treatments in ovarian cancer. In addition, there is a need to better target specific subsets of the disease based on histologies and genetic profiles instead of treating all ovarian cancers as a uniform disease, which is clear that it is not.[82] ERβ and GPER1, PR and its subtypes, and the GnRH receptor are also potential targets of hormone agents that provide opportunities for fine-tuning therapies. Standardization of the evaluation of their expression in the clinic is a prerequisite for their full exploitation as previously learned from the ER use in breast cancer. Eventually, one can envisage the use of a panel of well-standardized expressions of several hormone receptors to guide treatment of well-characterized ovarian cancer subsets as the optimal mean of obtaining the full potential of hormonal treatments. Development of a test based on the expression of a panel of estrogen-responsive genes correlating with the response to endocrine therapies could be an alternative or complementary strategy.[83]

An additional problem in cancer treatment with targeted agents consists of changes of the expression of the target with disease evolution. This is a well-documented issue in breast cancer and could be a cause of treatment failure with hormonal agents in ovarian cancer if receptor expression changes. In order to monitor receptor expression noninvasively, positron emission tomography/computed tomography with a fluoroestradiol tracer is under development.[84] This radiologic method could be additionally of particular value for the study of tumor heterogeneity by delineation of different areas of tumor that are positive or negative for the tracer in the same patient. Information on this aspect of individual tumor biology would be of interest for treatment planning and use of sequential treatments addressing parts of the cancer with differing biologies.

Tumor heterogeneity, either primary or secondary to treatment pressure, may relate to the presence or acquisition of molecular lesions leading to tumor resistance. Lesions commonly present in serous ovarian cancers have been characterized in whole-genome studies.[85] The most common molecular lesions in serous ovarian carcinomas, as discovered in these studies, involve mutations of tumor suppressor p53 and may interfere with the efficacy of hormonal therapies by promoting genetic instability that leads to the accumulation of additional mutations and resistance development.[85] Pathways emanating from growth factor receptors such as the Epidermal Growth Factor Receptor (EGFR) family and Insulin-like Growth Factor Receptor (IGF-IR) family as well as Notch and leptin signaling may promote ER signaling independent of ligands and also favor resistance to agents targeting it.[86,87]

Finally, development of combinations of hormonal treatments with other targeted agents is another therapeutic pathway to consider. Here again breast cancer leads the way with the introduction of combinations of hormonal therapies with mTOR or cyclin D inhibitors and the hope is that ovarian cancer could follow the paradigm.[88,89] Other agents that could be considered for combinations could be VEGF inhibitors or Poly-adenosyl Ribosyl Polymerase (PARP) inhibitors that have already been studied and shown activity in ovarian cancer.[90]

Author Contributions

Conceived the concepts: IAV. Analyzed the data: IAV. Wrote the first draft of the manuscript: IAV. Developed the structure and arguments for the paper: IAV. Made critical revisions and approved final version: IAV. The author reviewed and approved of the final manuscript.

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