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Revisiting the Role of Antiandrogen Strategies in Ovarian Cancer

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Explain the role of the androgen axis in the development of ovarian cancer.
2. Discuss the potential compounds with anti-androgen activity that can be assessed for the treatment of patients with ovarian cancer.

ABSTRACT

Androgen receptors are frequently expressed in epithelial ovarian cancer (EOC). Their role in the development of EOC is not fully understood. In the present review we first discuss the epidemiological data linking a hyperandrogen state to a higher risk for ovarian cancer, second describe in vitro studies of the role of androgens in influencing the growth of EOC, and finally review the completed clinical trials with compounds that exploit the androgen axis in patients with ovarian cancer. The therapeutic approaches that inhibit androgen signaling have so far produced only modest response rates. In the light of new data regarding the role of androgen stimulation in the evolution of EOC and the emergence of new compounds used for the treatment of other hormone-driven malignancies, such as prostate and breast cancer, we provide suggestions for new studies of antiandrogen therapeutics in the treatment of EOC. A specific example is the new agent abiraterone. In addition, we propose a panel of molecules that could be assessed as potential biomarkers that may aid patient selection for this approach in the future. ***The Oncologist*** 2011;16:1413–1421

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Introduction

The androgen receptor (AR) is a nuclear receptor that functions as an androgen-dependent transcriptional regulator [1, 2]. In its basal state, AR is inactive and is bound to heatshock proteins and other cellular chaperones. Upon activation by androgen hormones, it undergoes a series of events, including dissociation from the heatshock proteins, dimerization, and nuclear translocation. It then directly binds to specific hormone response elements in the promoter regions of target genes, resulting in upregulation of these genes [3].

In epithelial ovarian cancer (EOC), AR is expressed more often than estrogen receptor (ER) and has been reported to be detectable in up to 90% of cases using immunohistochemistry (IHC) [4]. In this review we aim to (a) summarize the evidence from epidemiological, clinical, and in vitro studies on the importance of androgens and the AR in relation to EOC, (b) give an overview of completed clinical trials that target the androgren axis, and (c) suggest ways to optimize the exploitation of the AR pathway in future clinical trials.

Epidemiological Data on Androgens and the Risk for EOC

In women, androgens are mainly synthesized in the adrenal glands, the ovaries, and adipose tissue, and they have an important physiological significance for bone and muscle growth and maintenance as well as cognitive function [1, 5]. There is a growing body of evidence supporting the notion that androgens influence proliferation of the normal ovarian epithelium and are a risk factor for EOC [6].

Epidemiological studies have attempted to correlate conditions that are associated with high circulating androgen levels in women with the risk for developing EOC. Such conditions include polycystic ovary syndrome (PCOS) and obesity.

PCOS affects up to one in five women of reproductive age and is characterized by polycystic ovaries, chronic anovulation, and ovarian hyperandrogenism [7]. Schildkraut and colleagues observed a 2.5-fold higher risk for EOC among women with PCOS in a retrospective study (seven cases with PCOS and 24 controls), although other studies did not report any association between PCOS and a higher risk for EOC [8, 9].

Obesity is another condition that affects the levels of circulating sex hormones. High body mass index (BMI) is well proven to be a risk factor for the development of endocrine-related cancers such as breast cancer (1.5× higher risk per 10 units of BMI) and endometrial cancer (3–4× higher risk per 10 units of BMI) [10, 11]. For EOC, however, the association with BMI is less pronounced, showing only a modestly higher risk of 1.1× per 10 units of BMI in some studies [12, 13], whereas other studies failed to detect any significant association [14–16]. Recently, a large epidemiological study, including 226,798 women from across Europe, showed a clear association between a high BMI and the risk for EOC (1.3× higher risk for obese women than for nonobese women) [17]. Overall, there is a moderate but robust association between high BMI and EOC.

Some retrospective case–control studies and case reports suggest that exogenous androgen intake raises the risk for EOC [18]. In a larger cohort analysis, 15 women reporting the use of testosterone supplementation had a 3.7-fold higher risk for developing EOC than the control group [9].

The Role of Genetic Polymorphisms of Androgen Pathways in EOC

We are now beginning to develop a better understanding of the role of androgens and their interaction with the AR in the progression and proliferation of ovarian neoplasms. The fact that the majority of EOCs maintain expression of the AR to a higher degree than estrogen or progesterone receptors suggests that the AR is involved in molecular signaling in EOC. For prostate cancer, which is well known to express AR and depend on AR signaling, there is evidence that, in addition to androgen levels, AR signaling can be dependent on polymorphisms of the receptor [19]. Exon 1 of the *AR* gene contains a polymorphic trinucleotide repeat, CAG, which varies normally in the range of about 8–31 repeats [19]. Interestingly, it has been shown in vitro that the number of the trinucleotide units correlates inversely with the transcriptional activity of the AR [20–22]. Moreover, epidemiological cohort studies have shown that a shorter CAG repeat length is associated with a greater risk for prostate cancer as well as earlier diagnosis [19], although recent reports in larger populations have failed to confirm these findings [23, 24]. Rodriguez-Gonzalez and colleagues showed an association between a shorter CAG repeat length and the aggressiveness of prostate cancer, which is characterized by greater prostate-specific antigen staining and a higher Gleason score [25]. These findings support the hypothesis that fewer CAG repeats are associated with greater AR signaling in prostate cancer, and with more aggressive forms of the disease. Based on these findings, several studies have determined CAG repeat length in cohort studies of healthy women and correlated the findings with the risk for developing EOC. Ludwig and colleagues reported a significant inverse correlation of a short CAG repeat length and a

higher risk for EOC [26], although a study by Terry and colleagues provides contradictory results [27].

Among patients with EOC, a short CAG repeat length in the *AR* gene at diagnosis was associated with a significantly shorter overall survival time than in patients with more CAG repeats [28]. More specifically, the overall survival time of patients with <19 CAG repeats ($n = 9$) was 5.5 months, versus 32.6 months for patients with >20 CAG repeats ($n = 68$). The combination of a high BMI and a short CAG repeat length was an even stronger prognostic marker for survival, suggesting that greater AR signaling promotes a more aggressive phenotype in EOC [29].

Polymorphism of the gene encoding cytochrome P450 17A1 (*CYP17A1*), the 7α-hydroxylase/17,20 lyase enzyme that is involved in the synthesis of androgens, namely, polymorphism A2, has been linked to susceptibility for developing EOC. Polymorphism A2 leads to the substitution of C for T in the promoter region of the gene [30], whereas the variant of this polymorphism has been hypothesized to alter promoter activity, increasing *CYP17* transcription and, subsequently, estrogen and androgen production [31]. This hypothesis was confirmed by a large study analyzing polymorphism A2 of *CYP17A1* in blood samples of a cohort of 225 women 1 year prior to diagnosis of EOC, compared with a matched control cohort [30]. Polymorphism A2, either homozygous or heterozygous, was found to be more frequent in women who developed EOC (69%) than in women in the control group (54%), and its presence was associated with a 1.86-fold greater risk for EOC [30]. Among women with EOC, this polymorphism was further associated with a worse prognosis than in patients with wild-type alleles [32]. However, the biological importance of the *CYP17* polymorphism remains unclear, because its presence is not always associated with higher levels of circulating androgens [33].

AR Signaling in EOC

The transactivational potential of AR is coregulated by AR-associated proteins that can enhance the potential of AR signaling [34]. Amplified in breast 1 (AIB1) and AR-associated protein 70 (ARA70), both AR-associated proteins, are overexpressed and/or amplified in EOC [34]. ARA70 is overexpressed in the majority of EOCs when compared with normal ovarian surface epithelium [35], whereas AIB1 is amplified in 25% of EOCs and is associated with ER positivity [36]. As is the case with the *AR* gene itself, AIB1 harbors polymorphic trinucleotide repeats (CAG) [34], with short repeat lengths associated with aggressive EOC [37].

A well-studied pathway by which AR might influence the growth of EOC is through the modulation of the sensitivity of transforming growth factor (TGF)-β, which is a potent inhibitor of epithelial cells [38]. In primary EOC cell cultures derived from patients' ascites, TGF-β exhibited a growth inhibitory effect [39]. This finding was confirmed by a study in malignant and nonmalignant ovarian epithelial cells in which TGF-β induced growth inhibition [38]. Furthermore, Evangelou and colleagues observed that treatment with dihydrotestosterone reversed the growth inhibitory effect by downregulation of TGF-β receptors I and II [38, 40]. Recently, it was further shown that the expression of several TGF-β pathway proteins (mothers against decapentaplegic family member 3 [Smad3], plasminogen activator inhibitor type 1, transcriptional co-activator with PDZ-binding motif) is associated with a response to cisplatin-based chemotherapy in patients with serous EOC [41] and that the TGF-β–Smad3 pathway might play an important role in mediating ovarian oncogenesis by enhancing metastatic potential [42]. However, the specific molecular mechanism and interactions between AR and the TGF-β pathway still need to be elucidated for EOC.

A second AR-associated pathway is the epithelial growth factor receptor (EGFR) signaling cascade. EGFR is a tyrosine kinase receptor and a therapeutic target for several human tumors [43]. Ligand binding to EGFR promotes EGFR homo- and heterodimerization with related ErbB family members such as the human epidermal growth factor receptor 2, activation of the catalytic intracellular tyrosine kinase domain, and phosphorylation of specific tyrosine residues of the receptor cytoplasmic domain. The latter leads to the stimulation of numerous downstream signaling cascades associated with cell growth and survival, angiogenesis, and tumor metastasis. In EOC, EGFR expression has been reported to be in the range of 10%–70% (with an average of 50%) [44] and *EGFR* amplification has been reported to be in the range of 1%–6% of cases [45]. Indeed, studies on prostate cancer cells suggest that there is crosstalk between AR and EGFR [46]. In EOC, higher EGFR expression levels were found in AR-expressing tumors than in tumors not expressing AR [47]. In addition, in ovarian cell lines greater AR expression was correlated with greater inhibition of phosphorylated EGFR and phosphorylated mitogen-activated protein kinase (MAPK) upon androgen treatment [48]. Taken together, these data suggest AR may interact with EGFR signaling by inhibiting downstream targets such as the phosphoinositide 3-kinase–AKT and MAPK/extracellular signal–related kinase kinase–MAPK pathways.

Microarray-based gene expression studies on EOC cell lines before and after androgen treatment were successful in identifying 121 genes that are significantly upregulated [49]. Among these genes, most of which regulate transcrip-

Table 1. Summary of completed clinical trials of antiandrogen treatments

Study	*n* of patients	Disease stage	Drug	PR (%)	SD (%)
Parmar et al. [51]	41	Recurrent	GnRH agonist	15	12
Kavanagh et al. [52]	18	Recurrent	GnRH agonist	22	11
Lind et al. [53]	30	Recurrent	GnRH agonist	7	17
Miller et al. [54]	25	Recurrent	GnRH agonist	4	60
Carnino et al. [55]	20	Recurrent	GnRH agonist	0	70
Marinaccio et al. [56]	32	Recurrent	GnRH agonist	13	16
Jager et al. [57]	40	Recurrent	GnRH agonist	0	3
Ron et al. [58]	14	Recurrent	GnRH agonist	0	57
Duffaud et al. [59]	68	Recurrent	GnRH agonist	0	16
Paraskeviciute et al. [60]	32	Recurrent	GnRH agonist	6	13
du Bois et al. [61]	37	Recurrent	GnRH agonist	0	11
Balbi et al. [62]	12	Recurrent	GnRH agonist	8	25
Vassilomanolakis et al . [66]	23	Recurrent	AR antagonist	4	8
Tumolo et al . [65]	32	Recurrent	AR antagonist	6	28
Levine et al. [69]	35	Consolidation	GnRH agonist + AR antagonist	NA	NA

Abbreviations: AR, androgen receptor; GnRH, gonadotropin-releasing hormone; NA, not available; PR, partial response; SD, stable disease.

tion, proliferation, and G-protein signaling, eight G-protein genes were validated using quantitative reverse transcription-polymerase chain reaction. The GTPase *Rab35,* which is involved in vesicle trafficking, was the most upregulated gene following androgen stimulation. Using immunohistochemistry, Rab35 was expressed in the majority of ovarian tumors (95%) and its expression levels were correlated with those of AR, suggesting that Rab35 might be useful as a biomarker of AR function [49].

Androgens might also increase the activity of telomerase through transcriptional (mRNA and protein levels) as well as through post-translational (phosphorylation) modulation, introducing another possible mechanism for androgen-related ovarian carcinogenesis [50].

Clinical Trials with Compounds Affecting the Androgen Axis

Only a limited number of clinical trials have assessed the efficacy of androgen manipulation in EOC. Most of these trials involved patients with recurrent EOC, with only one trial assessing antiandrogens as consolidation treatment. The compounds studied in the trials were either gonadotropin-releasing hormone (GnRH) analogs such as goserelin, triptorelin, and leuprolide or receptor antagonists that bind to the AR and prevent its activation, such as bicalutamide and flutamide.

Our review of the published literature indicates that 12 clinical trials, totaling 369 patients, have been performed in recurrent EOC patients with GnRH analogs (Table 1) [51–62]. The proposed mechanism of action of GnRH analogs in EOC is the desensitization or downregulation of GnRH receptors in the pituitary, resulting in a decline in gonadotrophin secretion and a subsequent reduction in gonadal steroids, including androgens, which act as tumor growth factors [63] (Fig. 1). Interestingly, recent data suggest that follicle-stimulating hormone (FSH) may be involved in an-

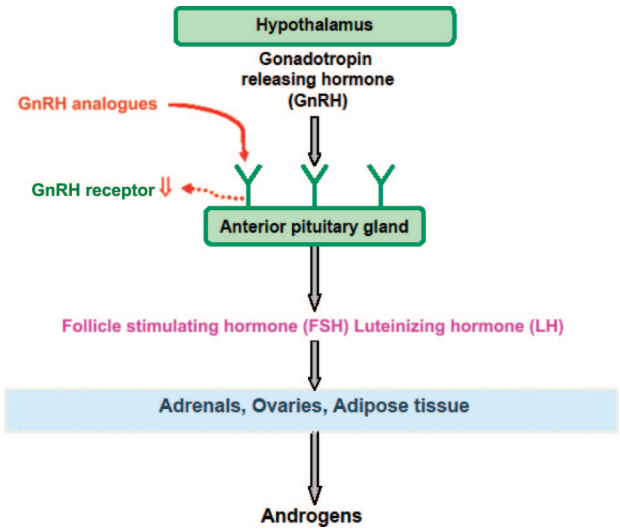

Figure 1. Gonadotropin-releasing hormone (GnRH)–gonadotropin axis. The proposed mechanism of GnRH analogs (goserelin, triptorelin) in epithelial ovarian cancer is thought to be desensitization or downregulation of GnRH receptors in the pituitary, resulting in a decline in gonadotropin secretion and subsequent reduction in gonadal steroids including androgens.

Table 2. Novel antiandrogen treatments currently in clinical trials

Drug	Properties	Tumor origin	Clinical trial stage	ClinicalTrials.gov identifier
MDV3100	AR antagonist	Prostate cancer	Phase III	NCT01212991
Abiraterone	CYP17 inhibitor	Prostate cancer	Phase III	NCT00638690
		Breast cancer	Phase I/II	NCT00755885
Orteronel	CYP17 inhibitor	Metastatic prostate cancer	Phase III	NCT01193257
TOK-001	CYP17 inhibitor and AR antagonist	Prostate cancer	Phase I	NCT00959959

Abbreviations: AR, androgen receptor; CYP17, cytochrome P450 17.

giogenesis, raising the possibility that GnRH analogs may impact ovarian cancer growth by additional mechanisms [64]. Combining the data from all 12 trials, a total of 21 (5.7%) patients achieved an objective response and 77 patients (21%) had stable disease (SD). It is difficult to interpret the high SD rate in the absence of randomized trials, and it could relate to the slow growth of a percentage of the tumors treated. Interestingly, in two studies, responses were observed in patients with well-differentiated tumors [51, 52]. However, it is not yet clear whether patients with low-grade ovarian tumors do represent a group more likely to benefit from treatments affecting the GnRH axis.

The AR inhibitor flutamide was assessed in two, nonrandomized phase II trials [65, 66]. Tumolo and colleagues reported a response rate (RR) of 6.3% ($n = 2$) and SD rate of 28% ($n = 9$) with a median SD duration of 24 weeks [65]. All patients were heavily pretreated (median of two chemotherapy lines) and had documented disease progression on screening. In a second trial by Vasillomanolakis and colleagues, 24 patients who progressed on chemotherapy received a low dose (100 mg three times a day) of flutamide [66]. One patient responded to the treatment (4.3%) and two patients had SD for ≥7 months.

In addition to the above, combination treatment with tamoxifen and GnRH analogs was evaluated in two phase II, single-arm clinical trials in patients with recurrent, chemotherapy-resistant EOC. The combination of tamoxifen and goserelin was assessed by Hasan and colleagues [67]. Those authors reported an RR of 11.8% (three of 26) and SD for >6 months in 10 patients (38.5%) with a combined clinical benefit rate (RR + SD rate) of 50% (13 of 26). The median progression-free interval was 4 months (95% confidence interval [CI], 2.4–9.6 months), whereas the median overall survival duration was 13.6 months (95% CI, 5.5–30.6 months). Treatment-limiting toxicity was not seen in any patient in the study population. There was no correlation between luteinizing hormone or FSH suppression and tumor response with the biomarkers assessed. Likewise, no relationship was observed between inhibin A or B and pro-α C levels and tumor response. In a similar trial, the same combination of tamoxifen and goserelin produced a high SD rate of 40% (10 of 25 patients) [68]. Interestingly, in both trials high SD rates were observed, which is disproportionate to the low RR reported. The high SD rate and the minimal toxicity make the combination of hormonal treatments an attractive option for future clinical trials, including those assessing consolidation strategies.

In this context, Levine and colleagues evaluated the combination of goserelin and bicalutamide in 35 patients with EOC in second or higher clinical disease remission [69]. The intervention produced a longer progression-free survival interval than in historical controls—11.4 months (95% CI, 10.2–12.6 months) and 10.7 months (95% CI, 9.3–12.2 months), respectively—but it did not reach the predetermined, clinically meaningful, endpoint set by the investigators (16.5 months). The proportions of patients remaining in remission at 6, 12, 18, and 24 months were 100%, 47%, 22%, and 13%, respectively. These data provide a useful benchmark for future trials, and the absence of significant toxicity confirms that effective hormonal therapy using a consolidation approach would be an attractive option.

In conclusion, the above data demonstrate that existing antiandrogen treatments have only a modest effect with potential benefit for only a minority of patients. Therefore, newer drugs that act on the androgen axis are needed in addition to better patient selection (Table 2). A drug that could be evaluated in clinical trials is abiraterone, which is a novel CYP17 inhibitor that irreversibly inhibits the generation of adrenal steroids downstream of CYP17 by blocking the conversion of pregnenolone to dehydroepiandrostenedione and progesterone to androstenedione (Fig. 2) [70]. Downstream of this reaction, it further suppresses the generation of estrogens and androgens [71]. The drug is well tolerated and it has been shown to have significant activity in patients with castrate-resistant prostate cancer, leading to a recently reported randomized phase III trial that provided positive evidence of the drug's efficacy in this disease [72]. Because

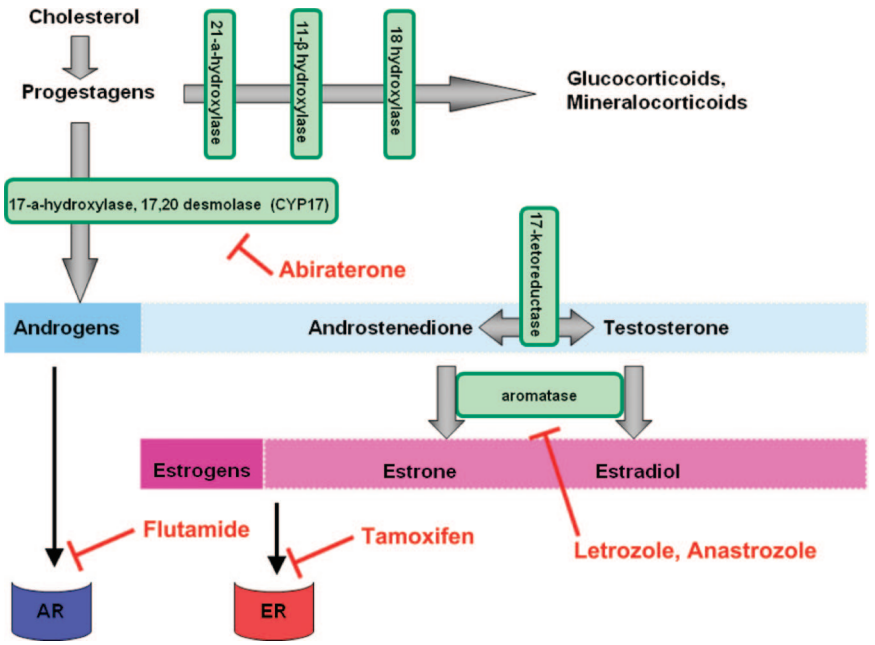

Figure 2. Steroid synthesis pathway and aromatization. Abiraterone is a novel cytochrome P450 (CYP)17 inhibitor that irreversibly inhibits the generation of adrenal steroids downstream of CYP17. It suppresses the generation of both androgens and estrogens. Flutamide competes with testosterone for androgen receptors (ARs), preventing their activation. Tamoxifen is an antagonist of the estrogen receptor (ER), blocking its downstream signaling. Anastrozole and letrozole block the production of estrogens by inhibiting the enzyme aromatase.

the steroid hormones upstream of aromatase and downstream of CYP17 could be important in the activation of ARs and possibly other nuclear steroid hormone receptors in EOC growth, abiraterone may impact EOC cell proliferation and survival by its androgen-suppressing activity. In addition, suppression of estrogens that might contribute to mitogenesis may add to the anti-tumor effect of abiraterone. Indeed, in a recent report of a phase I trial of abiraterone in women with hormone-resistant breast cancer, it was at a dose of 2,000 mg that all five patients had maximal suppression of estradiol and androgenic steroids. Two of 25 patients remained on treatment for >1 year, one with a confirmed partial response. The drug was well tolerated and a phase II trial is planned to start in 2011 [73]. We believe that the inhibition of the synthesis of both estrogens and androgens will have an additive effect. In addition, the low rate of side effects will allow patients to receive the drug for a longer time and derive the maximum possible benefit from it.

Discussion

EOC represents the most lethal gynecological cancer. Optimal surgical debulking followed by adjuvant chemotherapy has been the mainstay of primary treatment for many years. Unfortunately, the majority of women relapse and, despite the high RR achieved using chemotherapy for recurrent EOC, the prognosis remains poor. Newer treatments, such as bevacizumab or poly(ADP-ribose) polymerase (PARP) inhibitors for *BRCA* mutation carriers, were recently shown to improve upon the beneficial effects of chemotherapy and provide new therapeutic options [74, 75]. Hormone therapy that targets the estrogen pathway has also been assessed in patients with recurrent EOC [76–80]. The reported RR varies in the range of 0%–28% and the SD rate varied in the range of 20%–75% [79]. For example, letrozole was evaluated as therapy for biochemically only (cancer antigen [CA]125) relapsing patients following primary chemotherapy. It was demonstrated that patients with tumors expressing high levels of ER had a better response to letrozole, suggesting that the efficacy of hormonal treatment is dependent not only on the presence of relevant receptors but also on their quantity [78]. Another target for endocrine therapy is the AR. The rationale for further evaluation of antiandrogen treatment in patients with EOC includes the following.

First, most clinical trials evaluating the use of androgen blockade for the treatment of EOC have been small, nonrandomized studies involving patients with platinum-resistant disease. In this difficult-to-treat patient population, high rates of long-term SD have been reported and these results need to be validated in large, randomized clinical trials.

Second, those agents that have been tested for AR blockade in EOC, for example, flutamide, are known to be

weak AR antagonists. Newer promising treatments that are more potent suppressors of the AR axis or that inhibit androgen and estrogen synthesis should be evaluated in clinical trials for EOC. For example, abiraterone has been proven to be beneficial in prostate cancer patients who have progressed on previous treatment with GnRH analogs [81].

Third, most clinical trials assessing anti-AR strategies in EOC have not measured AR expression. The trials that did measure it used IHC, the results of which may not always reflect AR activity in EOC. We suggest the use of fluorescence in situ hybridization (FISH) to measure *AR* amplification in future trials of antiandrogen compounds in EOC.

The efficacy of antiandrogens in EOC patients in trials reported to date has been modest. All patients taking part in these trials had chemotherapy-resistant EOC and therefore represent a group with a poor prognosis. Similar results were reported in breast cancer patients with visceral metastases who received anastrazole (RR, 7%–14%) or exemestane (RR, 13.5%–25%) [82–85]. Endocrine treatment in breast cancer is generally more beneficial for patients with soft tissue metastases or low-volume disease. One way, therefore, of assessing the efficacy of abiraterone in ovarian cancer is to do randomized trials in asymptomatic patients with biochemically relapsing disease only (rising CA125).

Finally, patient selection is another important element that needs to be carefully addressed for a well-designed trial. Greater understanding of the contribution of androgens to the biology of EOC will assist with the selection of patients most likely to benefit from such treatments. Toward that end, we suggest as possible biomarkers: (a) the gene polymorphisms that correlate with AR activity, such as CAG repeats in exon 1 of the AR-encoding gene; (b) polymorphism A2 of *CYP17A1*; (c) measurement of *AR* amplification using FISH and its correlation with response to treatment; and (d) expression of AR pathway–associated genes such as *TGF-β*, *ARA70*, *AIB1, EGFR*, and *Rab35*. IHC quantification of Rab35 expression could be an initial starting point in this context. As suggested in the study by Smyth and colleagues, selection of patients according to percentage of tumor cells expressing hormone receptors might be more informative on the efficacy of a trial drug than patient selection based only on the presence or absence of the receptor [78]. We, therefore, suggest that correlation of the response to treatment with percentage of AR-expressing tumor cells also be assessed in future trials.

Conclusions

Antiandrogen compounds have been shown to have modest activity in patients with EOC, but data supporting their further evaluation are emerging. Newer, more potent compounds that block the synthesis of androgens and estrogens at the level of CYP17, such as abiraterone, could prove to be a useful addition to existing treatments. We suggest that the evaluation of abiraterone and other compounds with similar effects is worthwhile and should be undertaken within carefully planned clinical trials. In the light of evidence suggesting that ARs contribute to the mechanisms of EOC pathogenesis, patient selection should be aided by assessing potential biomarkers specific for that pathway.

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