Gynecologic Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

State of the Science

Hormonal strategies in gynecologic cancer: Bridging biology and therapy

HIGHLIGHTS

- Hormonal signaling is active in gynecologic tumors and involves tumor-stroma crosstalk.
- Progestins and aromatase inhibitors with mTOR inhibitors are clinically active in metastatic ER+/PR+ endometrial cancer.
- Systemic or local progestins enable fertility sparing in young women with early stage endometrial cancer.

1. Introduction

Upon ligand binding, the estrogen (ER) and progesterone receptors (PR) dissociate from chaperone proteins, dimerize, translocate to the nucleus and bind to specific chromatin sites [1,2] enhancing or repressing transcription in hormone dependent tissues. ER and PR are abundantly expressed in the female reproductive tract and mammary gland [3,4] and their expression levels and interaction with co-regulators dictate the robustness of signals, the specificity and context dependent actions in different tissues [5]. These events are tightly synchronized in individual cells and can be altered in the presence of mutations or epigenetic changes within cells or under the influence of the microenvironment. In the cancer setting, many of these mechanisms are altered causing the inability of ER and PR to appropriately act on the genome. ER and PR expression can be silenced by DNA methylation in endometrial cancer [6,7] and epigenetic modulators have been used to reverse PR transcriptional repression [8]. Recent evidence in breast cancer demonstrated the ability of PR to redirect ER to PR sites in the genome in response to estradiol and progesterone targeting PR responsive genes [9,10]. While such mechanisms have yet to be demonstrated in gynecologic cancers, the ability of PR to escort ER to PR sites may be a mechanism by which progestins oppose estrogen actions in the endometrium.

Signaling pathways, with which the receptors or co-regulators interact, influence responses to sex hormones. For example, activation of the AKT pathway due to alterations of PTEN, PI3K, or AKT, occurs in >90% of endometrial cancer [11]. Active Akt was shown to increase ERα transcriptional activity by increasing levels of phosphoSer167 on ERα in a $PTEN^{+/-}$ mouse model that develops endometrial tumors [12–15]. AKT activation also blunts PR action in endometrial cancer affecting gene expression, coregulator recruitment, and regression of endometrial tumors [16]. These findings have implications for designing active combinations.

Initiation and execution of hormonal signaling is tightly regulated by the crosstalk between cancer cells and the rich tumor microenvironment (TME) [17]. In the benign endometrium, it has been demonstrated that a complete estrogen and progesterone responses require a dynamic interaction between the endometrial epithelial glands and the stroma (Fig. 1). Experiments recombining epithelial and stromal compartments from ERα or PR knockout mice demonstrated the key role played by the stroma mediating epithelial cell proliferation in response to estrogen and progesterone [18]. Recent studies showed that stroma potentiates the response of endometrial tumors to progestins through paracrine signaling [19] and that deletion of PR in the stroma promotes progesterone resistance [20]. Aside from mediating progesterone effects, the enzyme aromatase responsible for local synthesis of estrogens, is highly expressed in the endometrial stroma [21,22] and promotes estrogen-induced tumor cell proliferation. Other components of the stroma are the immune cells, some of which express ER or PR and can be responsive to hormones [23]. Progestins have been shown to alter the outcome of infections at mucosal sites, in the genital, gastrointestinal, and respiratory tracts [24,25]. With the development of new agents targeting the immune system, it becomes essential to understand this component of the TME and the interactions between hormone and immune therapies.

2. Endometrial cancer (EC)

Unopposed estrogen is the most significant risk factor for type 1 EC and for its precursor, endometrial hyperplasia [26]. ER and PR expression is linked to grade of histological differentiation with 70%, 55% and 41% of grade 1, 2 and 3 endometrial tumors being ER+ and/or PR+, respectively [27]. The recent analysis of the Cancer Genome Atlas Project (TCGA) confirmed the presence of a hormonal phenotype cluster [16] characterized by increased expression of ER and PR and correlating with endometrioid histology [16]. Based on these observations, hormonal therapies including progestins and selective estrogen receptor modulators (SERMs) have been extensively investigated in EC. Response rates (RR) of 20–40% have been reported for high dose megestrol acetate in patients with recurrent or advanced EC, with highest benefit noted in women with grade 1–2 tumors [28]. The Gynecology Oncology Group (GOG) trial 81, randomized 299 patients to high or low doses of medroxyprogesterone acetate [28]. The lower dose was associated with improved median survival (11.1 months vs. 7 months) and RR (28% vs. 18%). Patients with grade 1 tumors had the best RR of 37% vs. 9% in patients with grade 3 tumors and responses strongly correlated with PR and ER expression [29]. One consequence of treatment with progestins is downregulation of PR [30]. On the contrary, tamoxifen was shown to increase PR expression in animal models [31]. As PR in the stroma acts in a paracrine manner to inhibit estrogen induced glandular epithelial cell proliferation [32], it was hypothesized that pretreatment with tamoxifen could increase the response of tumors to progestins. This concept was tested in a phase 2 trial alternating megestrol acetate with tamoxifen [32]. The RR to the combination was 27% and the overall survival was 14 months, with highest benefit

https://doi.org/10.1016/j.ygyno.2018.06.005

Please cite this article as: W. Nieves-Neira, et al., Hormonal strategies in gynecologic cancer: Bridging biology and therapy, Gynecol Oncol (2018), https://doi.org/10.1016/j.ygyno.2018.06.005

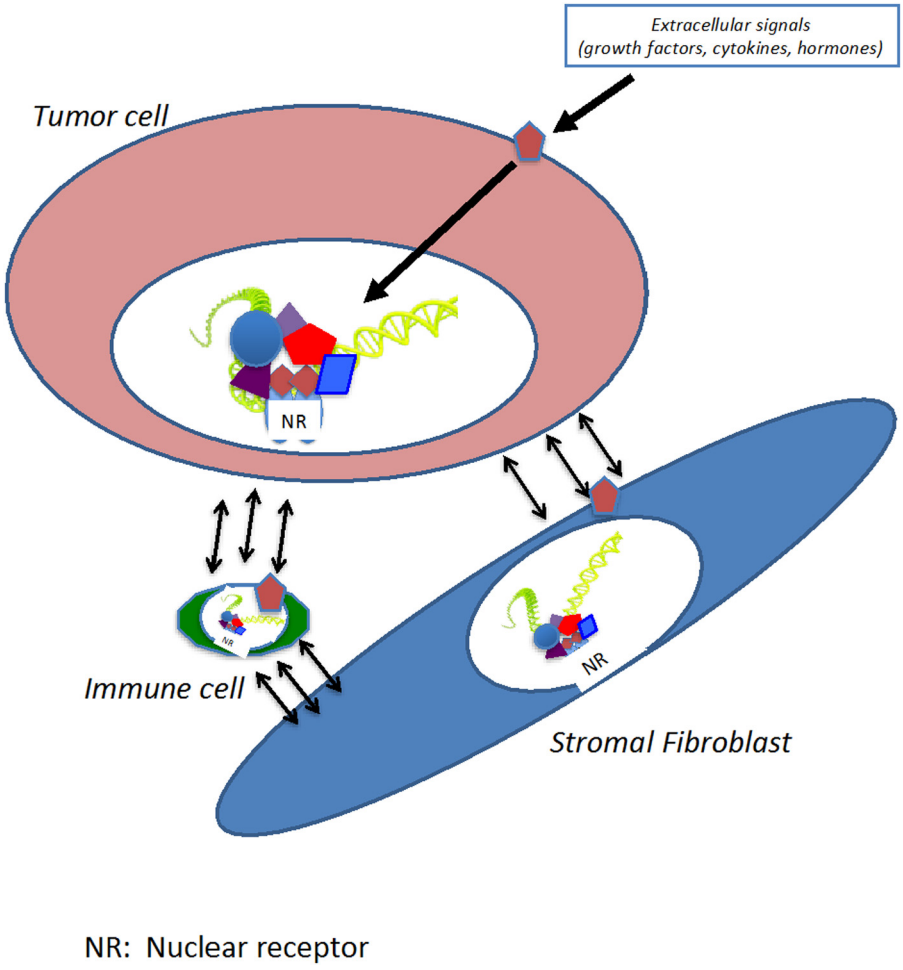

Fig. 1. Model illustrates hormone receptor function regulated by the cross talk between tumor cells and stroma.

observed again in patients with grade 1 tumors (RR of 38%). An important observation was that patients with lung only metastatic disease were among the best responders, highlighting the potential role of the TME in response to treatment.

The opposite strategy of reducing circulating estrogen by inhibiting aromatase or by direct inhibition of ER has been less successful. Although aromatase is expressed in the stroma of 60–70% tumors [33], the inhibitors anastrozole and letrozole have shown minimal activity in recurrent EC [34]. Likewise, tamoxifen yielded a modest RR of 10–20% in women with EC [35–36].

In an effort to improve the efficacy of hormonal interventions, combinations with agents targeting cross-talking signaling pathways have been investigated. Because the AKT/PI3K pathway is frequently altered in EC and AKT alters ER function [37], combinations of hormonal agents and mTOR inhibitors were tested. The combination of temsirolimus with megestrol acetate and tamoxifen caused a high incidence of venous thromboembolism and had modest activity, leading to premature termination of the trial [37]. However, the combination of everolimus and letrozole induced a clinical benefit rate of 40% and a RR of 32% in a phase 2 trial [38]. Patients with endometrioid histology and β-catenin mutations had best responses to the combination. An interesting observation was that among 9 patients with concomitant use of metformin either for treatment of pre-existing diabetes or protocol-related hyperglycemia the response rate was 56% (vs. 23% in non-users) [39]. These observations led to the recently reported randomized phase II GOG-3007 study comparing everolimus plus letrozole vs. the standard medroxyprogesterone acetate alternating with tamoxifen in patients with recurrent or metastatic EC. The clinical benefit rate was 78% with PFS of 6.3 months in the everolimus/letrozole arm compared to 69% with PFS of 3.8 months in the megestrol/tamoxifen arm [40]. In all, these data support the use of progestins alone or in combination with tamoxifen or of letrozole in combination with everolimus for patients with metastatic EC. Grade, ER/PR expression, presence of β-catenin mutations, and endometrioid histology were predictive of response. Rational combinations with HDAC or other epigenetic inhibitors or with inhibitors of cell cycle regulators (CDK) are being explored in ongoing trials.

3. Fertility sparing treatment of young patients

Approximately 5–10% of endometrial cancers develop in women younger than age 40. Most cancers are well-differentiated, ER and PR positive, early stage and fertility preservation represents a frequent concern. Conservative treatment with progestins is a safe and effective strategy in this context, with reported regression rates ranging between 70 and 85%. The Royal College of Obstetricians and Gynecologists compiled data from 13 series including 278 patients treated with progestins [41], reporting a regression rate of 75%. Although recurrence developed in up to a third of patients, they often responded to repeat treatment. A recent meta-analysis including data from 456 patients reported complete remission rate of 76.3%, recurrence rate of 30.7%, and a pregnancy rate of 52.1% [42]. Local treatment with a levonorgestrel releasing intrauterine device (LNG-IUD) is also effective and avoids side effects of systemic progestins. A systematic review and meta-analysis of oral progestins vs. LNG-IUD in patients with atypical endometrial hyperplasia reported a regression rate of 90% with the use of intrauterine devices

Please cite this article as: W. Nieves-Neira, et al., Hormonal strategies in gynecologic cancer: Bridging biology and therapy, Gynecol Oncol (2018), https://doi.org/10.1016/j.ygyno.2018.06.005