J Gynecol Oncol. 2019 Sep;30(5):e98
https://doi.org/10.3802/jgo.2019.30.e98
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Editorial

Aromatase inhibition in ovarian cancer: repeated signals of efficacy but tools for patient selection remain elusive

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▸ See the article "PARAGON (ANZGOG-0903): a phase 2 study of anastrozole in asymptomatic patients with estrogen and progesterone receptor-positive recurrent ovarian cancer and CA125 progression" in volume 30, e86.

Received: Jun 29, 2019
Accepted: Jun 29, 2019

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Many previous studies have investigated the role of endocrine agents in the treatment of ovarian cancer [1,2]. These studies have utilized a variety of compounds in heterogeneous patient populations at different points in the patient journey. While mixed signals have been generated by these studies the overall impression is of a therapeutic modality that although tolerable has at best moderate clinical activity within a small subset of patients. Reproducible methods for identifying this sensitive subpopulation remain elusive and as such the use of endocrine agents across the world is patchy and inconsistent.

The study of Kok et al. [3] investigated the response to anastrozole in 52 evaluable postmenopausal patients with asymptomatically relapsing oestrogen receptor (ER) or progesterone receptor (PR) positive epithelial ovarian cancer. The clinical benefit rate (CBR, defined as any response or stable disease at 3 months) was 35% with a median progression-free survival (PFS) of 2.7 months. The study also demonstrated that patients with a greater preceding treatment free interval experienced a longer median progression free survival on anastrozole. 22% of patients were on anastrozole for at least 6 months, sparing them the toxicity of systemic chemotherapy. Although these findings are in-keeping with previous research, there are a number of unique features of this trial that are worthy of further discussion.

Three aspects of the treatment setting chosen for this study are important. Firstly, given that endocrine therapy is likely to take longer to have a biological impact on cancer compared to cytotoxic chemotherapy [4] the recruitment of asymptomatically relapsing patients allowed the majority of patients to have the opportunity for this impact to be identified before the onset of symptoms and a necessity to switch to cytotoxic chemotherapy. Secondly, the fact that the study was restricted to patients with non-measureable or low volume recurrence would also serve to maximise the opportunity for an effect to be demonstrated. Thirdly, the fact that 93% of recruited patients had received only one previous line of chemotherapy would maximise the chance of demonstrating a signal of efficacy, as evidenced by previous studies which showed an inverse relationship between response to endocrine therapy and number of previous lines of chemotherapy [4,5].

Whilst these recruitment strategies were necessary in order to minimise the risk of stopping anastrozole before it had been given a chance to take effect, there is also a possibility that they contrived to select for patients with more inherently indolent disease, some of whom may have contributed to the CBR endpoint. Given that these strategies were employed, the partial response rate of 4% and 35% CBR at 3 months might be regarded as somewhat disappointing. In more heavily pre-treated patients a study of letrozole that also performed patient pre-selection based upon ER showed a response rate of 8% and a clinical benefit rate of 43% [6]. This latter study based selection upon the ER histoscore which is calculated by multiplying the intensity of staining (0 for none and 3 for intense) by the percentage of cells that have each level of staining to give a total with a maximum of 300. A number of previous studies have suggested that only patients whose tumor had a histoscore >150 had a reasonable chance of being endocrine sensitive and also there is a clear stepwise improvement in endocrine sensitivity above the histoscore 150 level with the tumors whose histoscore was 250–300 having a response rate as high as 15% and a CBR as high as 47% [4,6,7]. By contrast the Kok study [3] used a cut off of 10% cells showing any positive staining for either ER or PR. Some of these patients could have had an ER histoscore as low as 10 (or even 0 if their selection was based upon PR positivity). In fairness, the authors performed additional translational analyses looking at ER histoscore and percentage of ER positive cells and failed to demonstrate an association with outcome. The potential limitations of these secondary analyses were the low number of patients with material available for histoscore analysis (30/54; 56%) and the fact that the histoscores were calculated using tissue microarrays containing duplicate 1mm cores which may not have provided adequate reflection of the section or tumor as a whole. Interestingly, the investigators also performed PR assessment (a factor that has largely been overlooked in previous studies of endocrine therapy in ovarian cancer) and showed that 9 of the 12 patients (75%) who remained on anastrozole for at least 6 months were both ER and PR positive.

A further important factor that was historically overlooked in studies of endocrine therapy in ovarian cancer is the histological subtype. It is now very clear that these subtypes differ in terms of tissues of origin, molecular biology, chemosensitivity and clinical behaviour. It has also been shown that they have discrete ER and PR expression patterns and that the prognostic implications of the level of ER and PR differ between subtypes [8]. As such, it is likely to follow that the sensitivity to endocrine agents also differs between the histological subtypes. In the Kok study [3], the majority of patients (74%) had high grade serous ovarian cancer and the results should be interpreted within that context. Recently large retrospective studies have demonstrated the benefit of endocrine therapy in low grade serous ovarian cancer [9] and high grade serous ovarian cancer [4]. The low-grade serous study was particularly notable because it was able to compare first line hormonal maintenance with observation (following surgery and platinum-based chemotherapy) and demonstrate a benefit in terms of PFS for patients receiving maintenance endocrine therapy. Although selection bias is always a potential issue in such studies, in this case it could be argued that any such bias would likely result in a more favourable control group. It is important that future prospective studies of endocrine therapy in ovarian cancer are performed in a histological subtype specific fashion, although for rarer subtypes, international collaboration will be required.

In summary, the study of Kok et al. [3] again suggested the possibility of a subset of ovarian cancer patients benefitting from endocrine therapy in the context of low-level relapse with the consequent delay in initiation of more toxic therapeutic options. It also highlighted the

https://doi.org/10.3802/jgo.2019.30.e98

necessity to perform these studies within a histotype-specific context and the urgent need to hone down on better biomarkers. It is unclear whether more granular ER/PR biomarkers such as histoscore would be sufficient or whether multiparametric biomarkers including genomic factors will be required. What is clear is that as some patients derive significant benefit this research must continue, perhaps taking learnings from the breast cancer setting because if markers of sensitivity can be reliably identified then the possibility of utilisation in the first line adjuvant setting would remain a very attractive option.

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