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Letrozole may be a valuable maintenance treatment in high-grade serous ovarian cancer patients

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HIGHLIGHTS

- *ESR1* and ER expression are similarly high in HGSOC and in breast cancer.
- ER expression did not differ between platin-sensitive or –resistant HGSOC.
- ER expression did not differ between matched primary or recurrent HGSOC.
- Letrozole maintenance showed improved progression-free survival.

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ABSTRACT

Objectives. Endocrine therapy is used as maintenance in estrogen receptor (ER) positive breast cancers and has been proposed in low-grade serous ovarian cancers (LGSOC). Here we examine a rationale for its use as maintenance in high-grade serous ovarian cancers (HGSOC).

Methods. We accessed the TCGA PANCAN dataset to evaluate the expression of *ESR1*. *ESR1* expression data on all cancers (n = 8901) and HGSOC (n = 527) were followed by investigation of ER expression via immunohistochemistry (IHC) (n = 4071). The same was performed in an independent cohort for matched primary and recurrent HGSOC (n = 80). Finally, newly diagnosed ER + HGSOC patients were offered a maintenance therapy with Letrozole.

Results. ESR1 was strongly expressed in similar levels in HGSOC as in breast cancer. We found a strong ER expression via IHC in both the primary and matched recurrent HGSOC, particularly in the Platinum-resistant subgroup. The additional use of Letrozole as maintenance treatment was associated with a significantly prolonged recurrence free interval (after 24 months 60% when taking Letrozole *versus* 38.5% in the control group; $p = 0.035$; RFS: IC_{50} reached by one subject *versus* 13.2 months). This effect was also present in patients treated additionally with Bevacizumab; 20.8% of patients had no recurrence after 12 months compared to 87.5% when taking Letrozole in addition to Bevacizumab ($p = 0.026$).

Conclusions. Primary HGSOC have a slightly higher *ESR1* than and a similar ER expression breast cancer where aromatase inhibitor maintenance is routine for decades. Here we demonstrate evidence for the usefulness of Letrozole in HGSOC, particularly in patients with chemotherapy resistance or residual disease.

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1. Introduction

The prognosis of ovarian cancer is still poor, with a 5 year relapse rate of 75% for advanced HGSOC [1–3]. Despite better treatment options including maximal cytoreductive surgery and new-targeted therapies, the outcome has improved only marginally over the last decades,

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particularly in HGSOC. Therefore, several drugs have been evaluated in ovarian cancer in clinical trials in the primary and recurrent setting. The most promising agents so far are anti-angiogenesis inhibitors and PARP-inhibitors [4–9]. Bevacizumab, a VEGF-antibody, is approved for maintenance, based on a post-hoc analysis for high-risk cancers [10]. Olaparib, a PARP-inhibitor, is approved in Europe for patients with a germline BRCA mutation or BRCA mutated tumors in the recurrent setting after re-introduction of platinum-based chemotherapy [11]. In contrast, in the United States olaparib is approved for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer treated with three or more prior lines of chemotherapy [12]. Since 2016, two other PARP inhibitors, rucaparib and niraparib, are approved by the FDA [9,13].

Thus, there is an urgent need of new drugs as to improve outcomes, particularly by maintaining the status quo of these patients, without decreasing their quality of life. One important target with recent new and promising results as maintenance until time to next treatment (TTNT) is anti-hormonal therapy [14]. Several small case series demonstrated a benefit in ER+ ovarian cancer in particular in low-grade serous ovarian cancer (LGSOC) patients, suggesting that there are subgroups of patients with a specific tumor biology that responds very well to endocrine therapy [14]. Recently, Gershenson presented a retrospective analysis of endocrine maintenance therapy for LGSOC including 180 patients [15]. For patients receiving endocrine maintenance therapy (n = 66) after Platinum-based adjuvant chemotherapy, progression-free survival (PFS) was significantly better than for patients under observation only (n = 112, 64.9 months *versus* 27.3 months, $p < 0.001$). Most patients received treatment with Letrozole (54%) or Tamoxifen (28%). The same authors demonstrated already in 2012 in 69 patients with recurrent LGSOC who received 89 different hormonal therapy regimens a high clinical benefit rate. Patients receiving different regimens of endocrine maintenance therapy for relapse showed a response rate of 9% and stable disease of 62% [16]. Hereby, the rationale for endocrine treatment is based on the high ER/PR IHC expression as a predictive marker, since ovarian cancer is partly driven by the estrogen-pathway [17].

In one of the largest consortia studies (n = 2933), ER expression rate was between 20 and 90%, depending on the subtype, being high both in low grade and HGSOC (87% and 81%, respectively) [18]. The authors were able to demonstrate that strong ER expression in HGSOC was not significant for prognosis ($p = 0.49$). None of the previous trials and analysis on anti-hormonal treatment was ever done prospectively in the maintenance setting but rather as a treatment regimen in heavily pretreated patients, hereby mostly without providing information in regards to ER/PR expression.

2. Methods

2.1. Patient cohorts

Four patient cohorts are used for this analysis; (A) *ESR1* gene expression was measured in the publicly available US-American TCGA and the Australian Tothill datasets; (B) ER expression in HGSOC FIGO III/IV cancer patients was measured in another US-American cohort from Caris Life Sciences; (C) primary and matched recurrent HGSOC FIGO stage III/IV patients were examined for ER expression in 80 Swiss patients; and finally, (D) all newly diagnosed HGSOC FIGO III/IV with positive ER expression using IHC were prospectively included in our single-site Letrozole maintenance treatment approach at the University Hospital Basel, Gynecological Cancer Centre (Table 1).

The primary and matched recurrent HGSOC on tissue microarray (TMA, Cohort C), as well as all clinico-pathological data were collected from 1985 to 2002 as previously described [19] (Cohort C; Table 1). Time of recurrence was defined as symptomatic relapse confirmed by RECIST in the radiological examination. Cancers with a time to recurrence of less or equal 6 months after completion of platinum-based chemotherapy were defined as chemo-resistant.

2.2. TCGA data analysis

TCGA datasets were accessed through the UCSC Cancer Genomics Browser website [20,21].

ESR1 expression was analyzed using TCGA_PANCAN HiSeq_V2 dataset (Cohort A; Table 1). In regards to HGSOC, the TCGA (GSE68661 Affymetrix HAT Human Genome U133A Array [22]) and Tothill (GSE9899, Affymetrix Human Genome U133 Plus 2.0 Array [23]) ovarian cancer transcriptomic data sets were downloaded from Gene Expression Omnibus (http://www.ncbi.nlm.nih.gov/geo/).

2.3. Immunohistochemistry

ER expression of consecutive tissue samples (referrals from 2008 to 2016) submitted to a commercial CLIA-certified molecular profiling laboratory (Caris Life Sciences, Phoenix, AZ) was used for initial assessment (Cohort B; Table 1). The tissue diagnoses were submitted based on pathological assessment of physicians who requested the assays and were further verified by a pathologist at the Caris Laboratory. IHC was performed on formalin-fixed paraffin-embedded tumor samples using commercially available detection kits, automated staining techniques (Benchmark XT, Ventana, Tucson, AZ) and antibodies against ER (Clone SP1; Ventana, Tucson, AZ). Positive ER was defined as 2+ staining in at least 75% of tumor cells, or 3+ staining in at least 50% of tumor cells.

Table 1
Clinicopathological variables of patients with HGSOC in the various cohort.

Cohort	A	B	C	D	
Nationality	US	US	Swiss	Swiss	
Clinicopathological characteristics	TCGA PANCAN	ER IHC Caris	Matched primary/recurrent	Letrozole maintenance	No maintenance
Date of sampling (years)			1985–2003	2013–2017	2009–2017
Median age (years)			59	71.1	66.9
IQR			20–77	57.2–75.8	59–68.8
FIGO stage (%)					
I			0	0	0
II			3.7	0	0
III			96.3	60	75
IV			0	40	25
Number of patients	527	4071	80	23	27
Platinum-sensible			57	22	29
Platinum-resistant			23	1	2
Number of platin-containing cycles					
6 cycles (n, %)			73; 91.3	21; 91.3	25, 80.6
<6 cycles (n, %)			7; 8.7	2; 8.7	6; 19.4

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