

Endocrine Therapy in Epithelial Ovarian Cancer (EOC) New Insights in an Old Target: A Mini Review

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Abstract

Introduction: Endocrine therapy with tamoxifen and aromatase inhibitors has been used in Estrogen Receptor (ER) positive breast cancer for decades. Epithelial ovarian cancer, in particular serous Low- and High Grade Subtypes (LGSOC, HGSOC), shows a similar high ER expression and represents therefore a potential target for endocrine therapy. Many treatments have been evaluated in phase II clinical trials in heavily pretreated patients, but the overall tumor response and agent superiority (tamoxifen vs. aromatase inhibitors) remains unclear.

Methods: We present a literature review of endocrine therapy for ovarian cancer and emphasize the role of endocrine maintenance therapy with letrozole after standard of care.

Results: Endocrine therapy appears to be an eligible and cost effective treatment option with good quality of life in the adjuvant and recurrent treatment of advanced ovarian cancer. The trend shows the highest effect in histological subtypes with the highest ER expression (LGSOC and HGSOC).

Introduction

Ovarian cancer is the second most common, and most lethal gynecologic malignancy in developed countries. Worldwide, it accounts for an estimated 239,000 new cases and 152,000 deaths annually [1]. Epithelial Ovarian Cancer (EOC) is the most common histologic type (95%), with serous being the most common subtype (75% of epithelial carcinomas, with a further classification into High Grade Serous Cancer (HGSOC) and Low Grade Serous Cancer (LGSOC) [2,3] followed by endometrioid, clear cell and mucinous cancer.

Approximately 65% of all patients with EOC are diagnosed with stage III or IV disease, which partially explains the poor prognosis (5-years-survival 14-23%). The standard treatment recommendation for advanced disease in all histological subtypes includes optimal cytoreductive surgery followed by a combined chemotherapy with carboplatin and paclitaxel. However, despite high response rates, the prognosis remains poor and most patients will usually relapse within five years of initial diagnosis. There is an urgent need to develop new therapeutic strategies for primary and recurrent disease, as well as for maintenance treatment. To date, angiogenesis-inhibitors and PARP-inhibitors are approved for maintenance treatment. However, none of these drugs showed either a significant survival benefit or a better cure rate; therefore, future directions should focus on drugs that improve outcomes by maintaining the best quality of life and extending the length of remission.

Endocrine therapy has been routinely used for decades in adjuvant and recurrent breast cancer with a high efficacy at low costs. In the adjuvant setting aromatase inhibitors reduces the risk of recurrence by 40-50%. Evidence of the stimulating effect of estrogen and progesterone on ovarian cancer progression and metastasis has been demonstrated in previous studies [4] and the use of endocrine

treatment in ovarian cancer has been evaluated in several clinical phase I and II studies.

Methods

We did a comprehensive literature review including all phase I, II and III trials as well as meta-analysis and previous reviews related to endocrine treatment in ovarian cancer through computerized and manual searches.

Results

Estrogen and progesterone expression in ovarian cancer

Similar to breast cancer, the majority of ovarian carcinomas express estrogen receptors [5]. In a recent publication, we could demonstrate similarly high expression of ESR1 in ovarian and breast cancer and a strong ER expression in both primary and matched recurrent HGSOC, particularly in the platinum-resistant subgroup [6]. Estrogen is known to drive disease in ER positive breast cancer patients. Several preclinical models have demonstrated the role of estrogen in terms of tumor proliferation and progression in EOC through direct (tumor VEGF production via ER signaling) and indirect (increased cell migration via protein kinase signaling) pathways [4,7].

In one of the largest consortia studies by Sieh et.al [8] including more than 2,900 primary ovarian cancer samples, the expression rate of ER varied between 20-90%, depending on the ovarian cancer subtype: low-grade serous ovarian cancer 87%, high-grade serous ovarian cancer 81%, mucinous ovarian cancer 21%, endometrioid ovarian cancer 76% and clear cell ovarian cancer 20 % [8]. In high-grade serous cancers, a strong PR expression was associated with a significant better survival compared to lower PR expression. In

contrast, higher ER expression was not associated with significant better survival outcome. In a Chinese meta-analysis with more than 6,000 patients, higher ER expression was also not prognostic, in contrast to PR and HER2 expression [9].

Benefits of endocrine therapy in ovarian cancer

Since 1982, more than 50 trials evaluated the efficacy of endocrine therapy in ovarian cancer, but no controlled randomised studies have been reported to date. Almost all trials included patients with prior treatments. Overall, studies lack standardised analyses with inconsistency in the use of endocrine agent (mostly used: tamoxifen, letrozole, anastrozole, exemestane), poorly defined histological subtypes and ER expression as well as unclear prior therapeutic treatment, which may explain the inconsistency of the results. Positive hormonal receptor status (ER/PR) and histologic subtype seems to be of relevance when it comes to response to endocrine therapy [10-12]. Recently, in a meta-analysis involving 2490 patients, Paleari et al. [13,14] found a clinical benefit rate of 41% in EOC patients with endocrine therapy, suggesting that there are subgroup of patients with tumor biology that responds very well to treatment. Tamoxifen showed the highest clinical benefit rate (CBR) (43%) based on 23 studies, while the CBR for aromatase inhibitors in 10 studies was 39% [13].

Tamoxifen: Tamoxifen is a selective estrogen receptor blocker and its utility and safety have largely been proven in breast cancer. The first to describe its effect on ovarian cancer was Myers in 1981, and several Phase II studies have followed, listed in (Table 1) [14]. A meta-analysis demonstrated an objective response rate of 9.6% (60 out of 623 patients) with a variation between 0-56% and a clinical benefit rate of 32%, ranging from 0-100%. Stable disease for more than four weeks, was observed in 131 of 411 (31.9%) women. In 2010 the author updated the meta-analysis but was not able to give any evidence-based recommendations. An important note is that most of the patients in the mentioned trials were heavily pretreated and the ER status was not established, making a clear statement about the clinical benefit difficult. In a systematic review, Perez-Gracia et al. [15] found a response rate of 13% in a total of 648 patients while the stabilization rate was 38% [15]. A low response rate to tamoxifen was directly associated with the number of prior treatment: A response rate of 26% could be found when selecting the trials where most patients received no more than one prior therapy, whereas heavily pretreated patients showed a response rate of only 4%.

Study/year/country	No. of pts/no. of evaluable pts	Daily dose (mg)	CBR N (%)	Refractory/resistant to platinum
Schwartz PE, 1982, USA	13/13	20	5 (38.4)	Yes
Schwartz PE, 1989, USA	49/49	20	NR	No
Pagel J, 1983, Denmark	29/21	20	20 (95.2)	No
Shirey DR, 1985, USA	23/23	20 (11 pts) 40 (12 pts)	19 (82.6)	Yes
Rowland K, 1985, USA	9/9	40	0 (0)	NR
Hamerlynck JVTH, 1985, Netherlands	64/18	40	0 (0)	Yes
Landoni F, 1985, Italy	63/55	40	19 (34.5)	No
Campbell JJ, 1985, Australia	22/22	40	12 (54.5)	Yes
Slevin ML, 1986, UK	22/22	40	1 (4.5)	Mixed
Weiner SA, 1987, USA	37/31	20	9 (29)	NR
Quinn MA, 1987, Australia	40/40	40	21 (52.5)	NR
Osborne RJ, 1988, UK	53/51	40	1 (1.9)	Yes
Hatch KD, 1991, USA	105/105	40	58 (55.2)	NR
Ahlgren JD, 1993, USA	29/29	80 (days 1-30) then 40	23 (79.3)	Mixed
Losa G, 1993, Italy	55/55	40	23 (41.8)	NR
Jager W, 1995, Germany	37/33	30	23 (69.7)	Yes
van der Vange N, 1995, Netherlands	10/6	40	2 (33.3)	Yes
van der Velden J, 1995, Australia	30/30	40	12 (40)	NR
Gennatas C, 1996, Greece	50/50	40	28 (56)	Mixed
Marth C, 1997, Norway	155/65	30 or 40	54 (83)	Yes
Rolski J, 1998, Poland	47/47	40	25 (53.2)	NR

Trope C, 2000	66/55	30 or 40	55 (100)	NR
Benedetti Panici P, 2001, Italy	28/28 [#]	80 (days 1-30) then 40	19 (67.8)	Yes
	22/226	80 (days 1-30) then 40	18 (81.8)	No
Markman M, 2004, USA	14/14	80 for 1 month then 40	0 (0%)	Yes
Wagner U, 2007, Germany	56/56	40	16 (28.6)	Yes
Harteau JA, 2010, USA	70/70	40	5 (7.1)	Mixed
George A, 2017, UK	43/43	20 (36 Pts) 40 (7 pts)	28 (65.1)	Mixed

CBR, clinical benefit rate (CR + PR + SD), [#]Platinum-sensitive population, 'Platinum-resistant population.

Table 1: Clinical trials of tamoxifen in recurrent ovarian cancer.

Therefore, unselective treatment in the whole population of patients with EOC may underestimate the actual efficacy of endocrine treatment. In one of the largest tamoxifen trials with 105 patients, almost all patients with complete response had elevated Estrogen Receptors (ER) (89%). In contrast, only 59% had elevated ER when patients had low or non ER [16]. In a publication by Swartz et al., all patients with stable disease had ER positive tumors [17]. In this study, the role of concurrently given tamoxifen with chemotherapy was evaluated but no difference in Progression Free Survival (PFS) and Overall Survival (OS) was shown between patients on tamoxifen and those not receiving tamoxifen. One weakness of this study was that tamoxifen was administered for only 36 weeks. As mentioned, the latest meta-analysis published in 2017 reported an overall clinical benefit rate for tamoxifen of 43% in 53 trials examined.

Aromatase inhibitors (AI): Aromatase inhibitors reduce the conversion of androgens to estrogens by about 90% and are the key enzymes of in-situ estrogen metabolism in postmenopausal women. Its expression in ovarian cancer ranges from 33% to 81% [18]. The use of Aromatase Inhibitors (AI's) in ovarian cancer has been reported since the 1990's with a clinical benefit rate ranging from 20-65% (Table 2) [14]. Most recently, combined therapy with letrozole and the mTOR inhibitor everolimus in recurrent ER positive HGSOc showed a promising 12-week PFS rate of 47% [19]. A study by Bowman et al. showed that a high degree of ER expression was predictive of tumor marker CA125 responses and stabilization of disease [20]. Smyth had similar findings, enhancing the evidence that the degree of ER expression correlates with the response to endocrine treatment [21].

Study/Year/Country	No. of Pts/ No. of evaluable pts	Agent	Daily dose (mg)	CBRN(%)	Refractory/ Resistant to platinum
Ahlgren JD, 1993, USA	15/15	Aminoglutethimide	1000	3(20)	Mixed
Bowman A, 2002, UK	60/54	Letrozole	2.5	19(35.2)	NR
	60/50	Letrozole	2.5	10(20)	NR
del Carmen MG, 2003, USA	53/53	Anastrozole	1	23(43.4)	No
Papadimitriou CA, 2004, Greece	27/27	Letrozole	2.5	9(33.4)	Yes
	27/21	Letrozole	2.5	7(33.4)	Yes
Krasner CN, 2005, USA	35/23	Anastrozole	1	15(65.2)	NR
Verma S, 2006, Canada	24/22	Exemestane	25	9(41)	Yes
Tchekmedyan AK, 2006, USA	14/14	Letrozole	2.5	10(71.4)	NR
Kavanagh JJ, 2007, USA	13/13	Letrozole	2.5	9(69.3)	NR
	13/13	Letrozole	2.5	5(38.5)	NR
Smyth JF, 2007, UK	44/42	Letrozole	2.5	18(42.8)	Mixed
	44/42	Letrozole	2.5	17(40.5)	Mixed
Ramirez PT, 2008, USA	33/31	Letrozole	2.5	8(25.8)	Yes
George A, 2017, UK	54/54	Letrozole	2.5	30(55.6)	Mixed

Colon-Otero G, 2017, USA	20/19	Letrozole	2.5	NR	Mixed
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Table 2: Clinical trials of aromatase inhibitors in recurrent ovarian cancer.

Use of AI in LGOSC and HGSOC: Because of its high ER expression, low and high grade ovarian cancer subtype could particularly benefit from endocrine treatment. In a study on advanced LGSOC, Gershenson retrospectively analyzed 64 patients treated with letrozole, anastrozole and tamoxifen in recurrent EOC and showed an overall response rate of 9%, while 61% of the patient had a PFS of 6 months or greater, independent of the anti-hormonal agents [22]. Four years later, the same author analyzed the effect of hormonal maintenance therapy vs. surveillance in LGSOC after completion of primary therapy and found a significant benefit in the PFS with hormonal therapy (64.9 months vs 26.4 for matched surveillance patients (p=0.001) [23]. Most patients received treatment with letrozole (54%) followed by tamoxifen (28%). In a previous study, we could demonstrate the utility of letrozole for maintenance treatment following first line therapy with cytoreductive surgery and platinum-based chemotherapy in high grade ovarian cancer [6]. Patients treated with letrozole showed significantly prolonged recurrence free intervals in comparison to the control group. After 24 months, 60% of patients were progression free while taking letrozole vs. 38.5% in the control group; p=0.035). 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). The biggest effect was shown when letrozole was initiated in parallel to first line chemotherapy and the effect was similar in patients showing chemoresistance. The effect of endocrine therapy in platinum-resistant or refractory recurrent ovarian cancer has been demonstrated in the Paragon-Study, with a clinical benefit in 27% of the patients taking anastrozole [24]. The authors also demonstrated an improvement of quality of life in patients under this treatment.

Summary

The promising results of endocrine therapy in ovarian cancer with a clinical benefit up to 41%, in combination with the low cost and toxicity of the drug, offer a new and cost-effective therapeutic option in the adjuvant and recurrent setting. When selecting ER positive cancers, the effect seems to be even higher. These findings justify a routine determination of ER-status for all newly diagnosed ovarian cancers and, when positive, the initiation of endocrine treatment in the adjuvant and recurrent setting. This could significantly delay the time to next treatment and improve the quality of life.

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