

The efficacy of the second-line chemotherapy commonly used in both relapsed ovarian cancer patients and those with primary treatment failure remains unsatisfactory. This therapy has a small effect on survival, whereas associated toxicity may diminish the patient's quality of life.

Hormonal factors play a role in ovarian tumorigenesis, and inhibition of the stimulating effects of estrogens may exert a clinical benefit. The role of hormonal therapy as a palliative therapeutic alternative for ovarian cancer remains undetermined. This modality may result in long-term stabilization of disease in individual patients and less frequently in tumor remission.

In this article the role of hormonal factors and recent literature of various forms of hormonal therapy for ovarian cancer are presented.

Key words: ovarian cancer, endocrine therapy, estrogens, aromatase inhibitors.

The role of hormonal factors and endocrine therapy in ovarian cancer

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Introduction

Ovarian cancer is most frequently diagnosed at an advanced stage, is recurrent and is generally of poor prognosis. This primary is the fourth most common cause of female cancer death in Poland [1].

The efficacy of the second- as well as following lines of chemotherapy (CHT) used both in relapsed ovarian cancer patients and those with primary treatment failure remains unsatisfactory. Moreover, CHT associated toxicity may diminish the patient's quality of life. This treatment is administered until cancer progression or tolerance worsening occurs, and disease stabilization is regarded as a clinical benefit. Overall, an approximately 20–30% objective response rate, mainly with partial cancer regression, is observed with the second-line CHT.

In a randomized phase III trial of pegylated liposomal doxorubicin (PLD) and topotecan the response rate of 19.7% and 17%, median overall survival (OS) of 62.7 and 59.7 weeks and 3-year OS of 20.2% and 13.2% in a group of unselected recurrent or refractory ovarian cancer patients, respectively, were reported [2, 3]. In other studies of retreatment with a platinum compound and paclitaxel median progression-free survival (PFS) was 13 months [4] and 8.6 months [5], and the response rate was 30.9% [4] and 47.2% [5] among patients with the best prognosis, i.e. with relapsed platinum-sensitive ovarian cancer (patients who relapse 6 months or more after initial platinum/paclitaxel CHT).

Moreover, the response rate of 6.1% and 8.3%, median PFS of 3.6 and 3.1 months, and median OS of 12.7 and 13.5 months were obtained with gemcitabine and PLD, respectively, in patients with platinum-resistant ovarian cancer (patients whose disease recurs in less than 6 months after platinum-based therapy used in the primary setting) [6].

In this group of patients the respective 3-year OS was 13.8% and 9.5% with PLD and topotecan [2]. The duration of response obtained with consecutive lines of CHT was shorter, and the chance of response was decreased.

Chemotherapy associated toxicity, mostly hematological, including severe (grade 3 and 4), is present in approximately one third of cases, and may significantly diminish the patient's quality of life [4–6].

Unsatisfactory efficacy of CHT, and sometimes lack of other regimens to administer, encourage the search for a palliative therapeutic alternative for ovarian cancer.

In this article the role of hormonal factors and recent literature on various forms of hormonal therapy for ovarian cancer are presented.

The role of hormonal factors in ovarian cancer

There are some epidemiological, experimental and clinical data that suggest an important role of hormonal factors in ovarian carcinogenesis [7, 8]. Ovarian cancer risk is increased in nulliparity, and decreased risk of ovarian cancer is associated with younger age at pregnancy and first birth, the use of oral contraceptives and/or breast-feeding. Ovarian cancer may develop in

women previously treated for breast or corpus uterine carcinomas.

Despite the inconsistent data concerning a possible association between hormonal replacement therapy (HRT) and ovarian cancer risk, HRT, especially when it exceeds 10 years, was associated with 1.45–2.2 increase in relative risk of this malignancy [7, 9]. The risk could increase with the increased cumulative estrogen dose over time. Meanwhile, concomitant administration of progestin and estrogen may counteract the risk associated with estrogen use.

Studies *in vitro* and in animal models support data concerning estrogen's role in promoting epithelial ovarian tumor growth. Estrogen exerts its stimulatory effect mainly through the estrogen receptor (ER), which is present in 38–60% of epithelial ovarian cancer tumors [7, 10]. There are two types of ER, ER α and ER β (with opposite antiproliferative vs. pro-proliferative effects, respectively), encoded by different genes.

Low-level ER expression is associated with early stage and higher tumor differentiation. Endometrioid and serous tumors express higher levels of ER as compared to other histological types. Prolonged treatment with tamoxifen enables reduction of the expression of ER β in ovarian cancer cells [11].

The ER α form predominates in normal ovaries, the β form in normal ovaries and benign tumors. The exact role of particular forms of ER (and its variants), as well as the patterns of ER and progesterone receptor (PR) in ovarian tumorigenesis, the role of the response to endocrine therapy and the prognostic significance, continue to be under investigation [12, 13]. According to some authors, tumors of high PR expression and without ER have the best prognosis [13].

The mechanism of estrogen's mitogenic effect, and ER regulation of expression of several proteins in ovarian cancer, is not fully determined. The growth-inducing effect of estrogens is mediated mainly through nuclear ER α . The binding of estrogen to ER can increase or inhibit the transcription of many estrogen-responsive genes and their products (for example PR, cathepsin D, c-myc, bcl-2), which influence cell proliferation, tumor invasion and tumor responsiveness to endocrine therapy [7]. A mechanism of estrogen tumorigenesis not mediated by ER has also been suggested; both estrogen and its metabolites can directly damage DNA [14, 15]. Molecular factors that predict response to hormonal therapy and could help to identify patients who benefit the most from such treatment have been under investigation [16, 17].

Hormonal therapy in ovarian cancer

Selected phase II studies of hormonal therapy for ovarian cancer are shown in Table 1.

Selective estrogen receptor modifiers (SERMs)

The main mechanism of selective ER modulators function is their anti-estrogen effect through competitive combination with ER in ovarian cancer cells with a consequence of inhibition of estrogen/ER complex translocation into the nucleus. Tamoxifen, the main agent among SERMs, may also inhibit the activity of some polypeptide growth factors and conversion of estrone to estradiol. Novel SERMs include raloxifene, which has a smaller agonistic effect compared

to tamoxifen, and the pure (without any agonistic activity) ER antagonist fulvestrant.

Prolonged tamoxifen treatment stimulates ovarian steroidogenesis and thus increases the incidence of benign ovarian cysts in breast cancer patients, and in pre- or perimenopausal women with ovarian cancer [18]. In *in vitro* studies, however, tamoxifen inhibits ovarian cancer cell growth [19].

In clinical series ovarian cancer patients were administered tamoxifen at a daily dose of 20 to 40 mg (sometimes up to 80 mg) both as a single agent or concurrently with CHT. These studies mostly included heavily pretreated or platinum-resistant patients. The efficacy of concomitant use of tamoxifen and CHT was evaluated in phase II trials; however, owing to the limited accrual their results were inconsistent [20, 21]. According to some authors tamoxifen in advanced ovarian cancer has not been adequately evaluated in well-designed trials and its role may have been underestimated [20].

In relapsed ovarian cancer tamoxifen can produce an overall response rate of approximately 11–13% (range 0–56%), and disease stabilization in about 30% of patients (range 21% to 41%) [22–26]. Occasionally long-lasting cancer remission was observed. In the largest trial conducted by the Gynecologic Oncology Group (GOG) tamoxifen was used in 105 patients with stage III or IV ovarian cancer with persistent or recurrent disease after primary surgery and first-line CHT (some patients also received radiotherapy) [23]. The objective response rate of 17.1% including complete regression in 9.5% of patients was obtained. No cancer progression within 3 months in 50% of patients was reported in 38%. Clinical outcome for tamoxifen was not related to histological tumor type and patient's ER status. The reanalysis of the treatment results of 102 evaluable patients entered into this trial (95% had previously received platinum-based therapy, none paclitaxel) confirmed a similar objective response among cisplatin-sensitive and cisplatin-resistant patients: 15% and 13%, respectively [25]. For the whole group median PFS was 4.4 months (range 1.2–9.2 months).

The results of retrospective studies suggested that response rates for tamoxifen in less pretreated ovarian cancer patients seem better than those of heavily pretreated patients [20].

A combination of CHT and tamoxifen (as a CHT response modulator) in advanced ovarian cancer failing platinum-based CHT produced an overall response rate of 50% with a median duration of 8.5 months [27].

What is important, tamoxifen is safe and effective in cancer patients with renal dysfunction [26].

Disease stabilization was observed in half of patients treated for multiply recurrent epithelial ovarian cancer with fulvestrant; however, the median PFS was only 62 days [28].

Experimental data revealed that the SERMs (tamoxifen, raloxifene) can partially reverse multidrug resistance of ovarian cancer cells to anticancer drugs [29].

Aromatase inhibitors (AIs)

Aromatase inhibitors exert their effect through blocking aromatase – the enzyme complex that converts androgens to estrogens. This process, which is the major source of estrogen in postmenopausal women, is present in several normal

Table 1. Selected phase II studies of hormonal therapy for ovarian cancer

Study	Patients (No.)	Characteristics	Number of patients with platinum-sensitive tumor (%)	Treatment	Treatment response		
					RR (%)	PFS	OS
Ahlgren 1993 [22]	29	Stage III or IV refractory ovarian cancer (cisplatin-based CHT in 86%)	NR	Tamoxifen 40 mg bid for 30 days, then 20 mg bid	17	–	–
Bowman 2002 [39]	60 ^a	Recurrence after at least 1 CHT regimen	NR	Letrozole 2.5 mg/d	CR 0, PR 0, SD 20, Ca125 response (PR + SD) 35	Med. 35 w	–
Hasan 2005 [48]	26	Recurrence (3 CHT regimens in 50% of patients)	9 (35)	Tamoxifen 20 mg bid + Goserelin 3.6 mg/monthly	50; CR 3.8, PR 7.7, SD 38.5	Med. 4 mo.	Med. 13.6 mo.
Hatch 1991 [23]	105	Stage III or IV persistent or recurrent ovarian cancer after first-line combination CHT (platinum based in 92 patients)	NR	Tamoxifen 20 mg bid	CR 9.5, med. 7.5 mo. (max. 17 mo.) PR 7.6, med. 3 mo. (max. 9 mo.) SD 38, med. 3 mo. (max. 8 mo.)	–	–
Markman 1996 [25]	102	Stage III or IV, with refractory ovarian cancer after first-line combination CHT (platinum based in 97 patients)	20 (21)	Tamoxifen 20 mg bid	13 (15 and 13 in sensitive and refractory to platinum, respectively)	Med. 4.4 mo.	–
Papadimitriou 2004 [36]	27 ^a	Recurrence after at least 1 CHT (and tamoxifen in 33% of patients)	18 (67)	Letrozole 2.5 mg/d	15; CR 5, PR 10, SD 19 Ca125 response (CR, PR and SD in 4, 11 and 18, respectively)	17–33+ mo.	–
Ramirez 2008 [41]	33 ^{a,b}	Platinum- and taxane-resistant ER-positive ovarian cancer	–	Letrozole 2.5 mg/d	PR 3, SD 23 med. (PR+SD) 9 w	–	–
Smyth 2007 [40]	42 ^a	Previously treated ER-positive ovarian cancer progressed according to Rustin's criteria	23 (52)	Letrozole 2.5 mg/d	PR 9, SD 42 (med. 12 w) Ca125 response 17	≥ 6 mo. in 26% of patients	–

CHT – chemotherapy; NR – not reported; RR – response rate; CR – complete response; PR – partial response; SD – stable disease; PFS – progression-free survival; OS – overall survival; ER – estrogen receptor; Ca125 response – response using Rustin's Ca125 criteria; platinum-sensitive disease – recurred > 6 months after cessation of platinum-based treatment

^asome patients without objective response; ^b4 patients with peritoneal cancer

tissues including peripheral adipose tissue, muscles, liver, and also in the tumor. Intratumoral estrogens derived from *in situ* aromatization may function as autocrine growth and mitogenic factors that prompt cancer cell proliferation independently of circulating estrogen. Estrogen synthesis in the tumor is decreased by blocking intratumoral aromatase. Aromatase expression, which might be useful for identifying the subgroup of patients who may respond to AI therapy, was found in 33–81% of ovarian cancer tissues [30, 31]. Endometri-

oid cancer tends to express higher levels of aromatase, which suggests that patients with that subtype more than those with other histotypes of ovarian cancer may benefit from AI therapy [30].

An inverse correlation between aromatase and ER α was reported [32]. The correlation of aromatase activity with PR in ovarian cancer was reported, but no significant differences in aromatase expression depending on tumor histotype, cancer cell differentiation and survival were found

[30, 32–34]. The potential role of follicle-stimulating hormone (FSH), luteinizing hormone (LH) and other factors contributing to AI efficacy remains under investigation [7].

Data concerning potential predictive markers, useful for identifying those patients who have AI-sensitive tumors, have been studied, but the findings have been conflicting; in most studies there was no association between ER and PR and ovarian tumor response to AI therapy [7, 35, 36].

Preclinical studies demonstrated that exemestane enhanced the treatment effect of paclitaxel on aromatase-positive ovarian cancer cells, and pretreatment with formestane increased the sensitivity of human tumor cells to cellular cytotoxicity [37, 38].

Importantly, some data suggest that AIs might be particularly useful for prolonging the intervals during which patients with recurrent ovarian tumor do not require platinum treatment; the longer the platinum-free interval, the more likely it is that the tumor will respond to platinum retreatment [7].

A stable disease rate of 19%, and complete and partial response rates of 5% and 10%, respectively, were achieved with letrozole treatment for relapsed epithelial ovarian cancer [36]. Others reported disease stabilization in 20% of patients, and Ca125 responses in 26% [39]. Using Ca125 criteria, Ca125 stable/responding disease was linked to higher levels of ER, in particular ER α , and epidermal growth factor receptor, and lower erbB2 [39, 40]. The use of letrozole in patients with recurrent platinum- and taxane-resistant ER-positive high-grade ovarian tumors resulted in achieving the median duration of clinical benefit (partial remission and stable disease in 3% and 23% of patients, respectively) of 9 weeks [41]. In this group of patients, no progression (doubling of Ca125) following 6 months on letrozole treatment was reported in 26% [40].

Gonadotropin-releasing hormone (GnRH) analogues

The GnRH analogues are synthetic gonadotropin agonists that act by binding with their receptors in the pituitary, resulting in a decline in both LH and FSH gonadotropin secretion. Subsequent reduction of gonadal steroids, which serve as tumor growth factors, causes reversible pharmacological castration. According to Polish authors, goserelin addition to post-operative CHT and RT may have a positive impact on survival in stage III and IV ovarian cancer patients [42]. In cases with chemo-refractory tumors, after two lines of therapy this hormonal agent produced partial remission in 17% and disease stabilization in 30% with respective median PFS of 8.5 and 5.3 months [43]. Others reported disease stabilization in 16% of patients treated with triptorelin [44]. Lastly, in a prospective placebo-controlled study with advanced ovarian cancer patients, the addition of triptorelin to CHT had no impact on outcome [45]. No advantage of leuprorelin in platinum-refractory ovarian cancer was found in other studies [46, 47]. However, complete cancer remission lasting for over three years was observed occasionally, with GnRH agonist analogue therapy [47].

Similarly to other primaries, the concomitant administration of GnRH analogue and tamoxifen was explored

[48, 49]. Complete estrogen deprivation in platinum refractory or recurrent ovarian cancer revealed cancer stabilization that lasted for at least 6 months in 50% of cases [48]. There were cases treated with goserelin and tamoxifen with no disease progression for over two years [48, 49]. The use of goserelin and bicalutamide did not appear to prolong PFS in patients with epithelial ovarian cancer who were in the second or greater complete disease remission after CHT [50].

Opposite to CHT, endocrine therapy was well tolerated in the vast majority of patients. An additional benefit associated with endocrine therapy is its oral form and relatively low cost.

Unfortunately, endocrine therapy for ovarian cancer is not refunded in Poland. Current recommendations of the NCCC (National Comprehensive Cancer Network) classify endocrine therapy with anastrozole, letrozole, leuprorelin, medroxyprogesterone acetate and tamoxifen as a potentially active treatment option used in conjunction with CHT in recurrent disease [51].

In conclusions, the therapy of platinum-resistant and recurrent ovarian cancer has, in almost all cases, palliative intent. In this situation therapy tolerance and patient's quality of life are of main importance.

Endocrine therapy may be a palliative therapeutic alternative for selected ovarian cancer patients. This method might be considered particularly in patients with contraindications to CHT and those in whom we terminate cytotoxic treatment. With endocrine therapy disease stabilization was usually achieved. However, occasionally, this treatment produces long-term objective cancer remission. Research for prognostic factors associated with most benefits of endocrine therapy which may allow a better selection of patients for this therapy are justified. Moreover, the verification of endocrine therapy efficacy in well-designed trials is required.

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