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EDITORIAL

Recurrent epithelial ovarian cancer and hormone therapy

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Abstract

The role of hormone therapy in the treatment of ovarian cancer is not clear. Data on the efficacy and safety of antiestrogens and aromatase inhibitors in recurrent ovarian cancer have been accumulated through phase Ⅱ clinical studies. Most of these studies were conducted in platinum-resistant recurrent ovarian cancer, and although complete response rates were not high, reported adverse events were low. If administered to patients who are positive for estrogen receptors, hormone therapy may become a viable option for the treatment of recurrent ovarian cancer.

Key words: Recurrent ovarian cancer; Hormone therapy; Letrozole; Anastrozole; Tamoxifen; Fulvestrant

Core tip: If administered to patients who are positive for estrogen receptors, hormone therapy may become a viable option for the treatment of recurrent ovarian cancer.

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INTRODUCTION

Hormone therapy for ovarian cancer is not mentioned in the Treatment Guidelines for Ovarian Cancer 2010 Edition and the role of hormone therapy for treatment of ovarian cancer in Japan is not clear. In the NCCN guidelines (ver. 3 2012), hormone therapy is classified under "other drugs that are potentially effective" as "approved treatment for recurrent forms" of epithelial ovarian cancer, which include anastrozole (aromatase inhibitor), letrozole (aromatase inhibitor), leuprorelin acetate (Gn-RH analog), megestrol acetate (synthetic progestin, not approved in Japan) and tamoxifen (antiestrogen). However, information on the efficacy of these drugs for recurrent ovarian cancer come from phase Ⅱ studies or retrospective studies, and the evidence level is not very high. Recently, a phase Ⅲ randomized comparative study of thalidomide and tamoxifen in patients who had marker recurrence after initial complete remission of stage Ⅲ and Ⅳ ovarian epithelial cancer, fallopian tube cancer, or peritoneal cancer was conducted[1]. However, due to the increased risk of death among the thalidomide group and the increased incidences of adverse events, the study was prematurely discontinued and the efficacy of tamoxifen was to be determined based on comparative studies with an untreated group or other drugs[1]. Here, we review the antiestrogens (tamoxifen, fulvestrant) and aromatase inhibitors (letrozole, anastrozole) with relatively large amounts of data on their efficacy in recurrent ovarian cancer.

OVARIAN CANCER AND HORMONE THERAPY

Several risk factors are involved in the development of ovarian cancer. The most certain risk and preventive fac-

tors are estrogen replacement therapy, obesity and oral contraceptives[2]. The estrogen hypothesis assumes that ovarian cancer is caused by the exposure of ovarian surface epithelium to estrogen, which supports the identification of an increase in estrogen converted from androgen by increased aromatase in the adipocytes due to obesity as a risk factor. Since the use of oral contraceptives suppresses the production of estrogen, it is consistent as a preventive factor. In a nurse health study conducted between 1976 and 2002, 82905 post-menopausal women including 389 ovarian cancer patients were enrolled, and a prospective observational study was performed[3]. Women who were receiving hormone replacement therapy with estrogen alone had a significantly increased risk-by 1.25 fold-of developing ovarian cancer, and it was reported that coadministration with progesterone could reduce the risks[3].

Estrogen stimulates tumor growth *via* estrogen receptor (ER). In a recent large-scale study, 36% of ovarian cancers were positive for ER[4]. Antiestrogens such as tamoxifen block the ER pathway, and aromatase inhibitors inhibit the synthesis of estrogen itself. In theory, both antiestrogens and aromatase inhibitors should exhibit antitumor effects against ovarian cancer. ER activates expression of genes involved in cell survival and proliferation, thus promoting tumor growth and progression, while the function of ER has been found to be antiproliferative and pro-apoptotic[5]. Growth response to estrogen in hormone responsive ovarian cancer cell lines was shown to be mediated by ER and not by ER[6,7]. A better understanding of ER signaling in ovarian cancer will permit refinement of combinations of targeted therapy with standard hormonal agents to improve treatment[8].

ANTIESTROGENS (TAMOXIFEN, FULVESTRANT)

Tamoxifen is an antiestrogen for which many phase Ⅱ studies in recurrent ovarian cancer have been conducted between 1980 and 2000. In the GOG study performed in 1991, 105 recurrent ovarian cancer patients including those with platinum-sensitive and resistant cancer received oral tamoxifen 20 mg/d as second line chemotherapy[9]. The complete response (CR) rate was 17%[9]. The disease control rate (DCR) including stable disease (SD) was 55%[9]. The rate of ER detection was 59% in partial response (PR) and SD and 89% in CR, which demonstrated a correlation between ER expression and tamoxifen treatment response[9]. Based on this study, the CR rate reassessed for platinum-resistant recurrent cancer patients was 13%[10]. In a review by Tropé *et al*[11] that includes the results of their own studies, in 647 recurrent ovarian cancer patients, the CR rate of tamoxifen was reported to range from 0% to 56%, with a mean CR rate of 11%. There are inconsistencies between reports on the correlation between ER expression and tamoxifen treatment response[12,13]. Meanwhile, a phase Ⅱ study was performed in which fulvestrant, a new antiestrogen approved for the treatment of postmenopausal hormone sensitive progressive/recurrent breast cancer, was used for the treatment of recurrent ovarian cancer[14]. Twenty-six recurrent ovarian cancer patients who had received a regimen of, on average, 5 types of anticancer drugs received muscular injection of fulvestrant 500 mg on day 1, 250 mg on day 15, and 250 mg on day 29. When this was repeated over a 28-d cycle, the CR rate was 8%. However, DCR including SD was 50%, and the median time to progression was 62 d[14].

AROMATASE INHIBITORS (LETROZOLE, ANASTROZOLE)

From 2000, there are reports of phase Ⅱ studies on aromatase inhibitors in recurrent ovarian cancer. The first report is by Bowman *et al*[15] on a phase Ⅱ study of letrozole. When 50 recurrent ovarian cancer patients received letrozole 2.5 mg/d orally, although there was no CR or PR, 10 patients maintained SD for 12 wk. ER was significantly higher in the tumors of SD patients than in the PD group[15]. Another phase Ⅱ study examined the effect of letrozole by accumulating only the cases of ER-positive recurrent ovarian cancer. In a study by Smyth *et al*[16], 42 ER-positive recurrent ovarian cancer patients received letrozole 2.5 mg/d orally. Of the 33 patients who had a measurable lesion, 3 patients (9%) achieved PR and 14 patients (42%) maintained stable disease state for 12 wk[16]. The study showed a positive correlation between the level of ER expression and treatment response[16]. In a similar study where ER-positive recurrent ovarian cancer patients received letrozole 2.5 mg/d orally, clinical benefit (PR or SD) was observed in only 26% of patients[17]. Meanwhile in another study in which 27 recurrent ovarian cancer patients, regardless of ER expression, received letrozole 2.5 mg/d orally, 1 patient (4%) achieved CR, 3 patients (11.1%) had PR, and 5 patients (18.5%) had SD, with DCR in 33.6% of patients, although no correlation was found between ER expression and treatment response[18]. In a phase Ⅱ study in which 53 recurrent ovarian cancer patients received anastrozole 1 mg/d orally, only 1 patient had PR, and SD over 90 d was observed in 42% of patients[19]. This study also could not find any correlation between ER expression and treatment response[19].

Reasons for the inconsistencies in the correlation between DCR value/ER expression and treatment response in the reports of antiestrogens and aromatase inhibitors include the small numbers of enrolled patients, differences in patient backgrounds including past treatment histories, and differences in the method of measuring ER. Based on the DCR, antiestrogens and aromatase inhibitors may both become an option in the treatment of recurrent ovarian cancer. However, in the future, it is important to examine the efficacy of these

Table 1 Therapeutic effect of antiestrogens and aromatase inhibitors on relapsed ovarian cancer *n* (%)

Ref.	Agents	Dose and usage	The kind of study	No. of patients	CR
Schwartz *et al*[12]	Tamoxifen	Oral 20 mg daily, maximun is 3210 mg	Phase Ⅱ	13	0
Weiner *et al*[13]	Tamoxifen	Oral 40 mg for 7 d, then 20 mg *po* daily	Phase Ⅱ	31	1 (3.2)
Hatch *et al*[9]	Tamoxifen	Oral 20 mg daily	Phase Ⅱ Platinum sensitive/resistant	105	10 (9.5)
Tropé *et al*[11]	Tamoxifen	Oral 30 mg or 40 mg daily	Phase Ⅱ Platinum sensitive resistant	66	2 (3)
Argenta *et al*[14]	Tamoxifen	Day 1500 mg *im* day 15250 mg *im* day 29250 mg *im*	Phase Ⅱ Platinum sensitive resistant	26	1 (4)
Bowman *et al*[15]	Letrozole	Oral 2.5 mg daily	Phase Ⅱ	50	0
Papadimitriou *et al*[18]	Letrozole	Oral 2.5 mg daily	Phase Ⅱ Platinum sensitive/resistant	27	1 (4)
Smyth *et al*[16]	Letrozole	Oral 2.5 mg daily	Phase Ⅱ Platinum sensitive/resistant	33	0
Ramirez *et al*[17]	Letrozole	Oral 2.5 mg daily	Phase Ⅱ Platinum resistant	31	0
del Carmen *et al*[19]	Letrozole	Oral 1 mg daily	Phase Ⅱ	53	0

CR: Complete response.

drugs in hormone receptor positive ovarian cancers in a greater sample size with a more homogenous patient background.

ADVERSE REACTIONS IN HORMONE THERAPY

Very few adverse events have been reported in phase Ⅱ studies. The number of serious adverse events (grade 3 and 4) is extremely small. In studies of antiestrogens, the only adverse events observed were deep vein thrombosis in 1.4% of patients, and grade 3 gastrointestinal symptoms in 1.4%[1]. There were relatively greater occurrences of nausea, vomiting, hot flush, arthralgia and malaise; however, the symptoms were mild[1]. In studies of aromatase inhibitors, there were no grade 3 or 4 adverse events, and adverse reactions, which included hot flush, sweating, malaise, queasy, and headache, were mild[16-19]. The incidence of arthralgia was relatively low[19].

INDICATIONS AND ADMINISTRATION OF HORMONE THERAPY IN OVARIAN CANCER

With antiestrogens and aromatase inhibitors, there are few occurrences of adverse events, and tolerability is high. Therefore, even if the general conditions are not favorable, unlike cytotoxic anticancer drugs, hormone drugs are beneficial in that they can be used over a relatively long period. In Japan, hormone therapy is not mentioned in the guidelines of ovarian cancer, however, it is likely to provide an option treatment which is not the treatment for cure but to prevent the progression of the disease for the recurrent ovarian cancer patients who have already been treated with various anticancer drugs and have no alternative treatment.

Evidence for hormone therapy for the treatment of ovarian cancer has been established from small-scale phase Ⅱ studies (Table 1). In many of these clinical studies, patients were not selected based on the hormone receptors in their ovarian cancer, and since patient backgrounds were different, this may be affecting the response rate to hormone therapy and masking its clinical benefits. It is desirable that prospective clinical studies in tumors with confirmed hormone receptors be planned to establish the effects and the role of hormone therapy.

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