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Review Article

Hormone therapy for patients with advanced or recurrent endometrial cancer

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Abstract

The "gold standard" treatment for endometrial cancer is completely staged surgery, followed by radiation or chemotherapy, based on the final pathological surgical stage and requirements. In the primary treatment of endometrial cancers, hormones are rarely taken into consideration after primary surgery. Primary treatment with hormones to preserve fertility in younger women with endometrial cancer is an attractive option, and many successful cases have been reported, although the majority of them finally received definite therapy, including total hysterectomy. The role of hormone therapy is often delayed in recurrent disease; response rates to progestins and tamoxifen or aromatase inhibitors in advanced/recurrent endometrial cancers are approximately 15–20% and nearly ≤10%, respectively. This review is focused on updated information and recent knowledge on the use of hormones in the management of women with advanced or recurrent endometrial cancers.

Keywords: advanced endometrial cancer; estrogen; hormone therapy; progesterone; recurrent endometrial cancer

1. Introduction

Uterine corpus cancer is the second most common cancer in the United States,[1] and its incidence has significantly increased in Taiwan in recent years.[2] Uterine corpus cancer includes endometrial cancer and uterine sarcoma, based on the distinguishing characteristics of the uterus. On the basis of biological and histopathologic variables, endometrial cancer can be further broken down into two major types, namely, Type I and Type II. Type I is strongly associated with unopposed estrogen, whereas Type II is relatively unrelated to the overproduction of estrogen.[3] In this review, we focus on the role of hormone therapy in the management of patients with advanced or recurrent endometrial cancers.

First, a brief introduction to endometrial cancer is required, for the purpose of identifying the potential population that may be benefited by hormone therapy.

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2. Endometrial cancer

Detailed information on endometrial cancer has been extensively reviewed in the past.[3] In brief, two types of endometrial cancer can be clearly defined, based on the distinct biological and histopathological findings (Table 1). Type I endometrial cancer includes the following characteristics: estrogen-related tumor, favorable outcome, well-known cancer transformation, and positive immunohistochemical staining for the phosphatase and tensin homolog gene and hormone receptors.[3] By contrast, Type II endometrial cancer comprises different characteristics, including an older population, little association with estrogen, unusual histological subtypes with p53 mutations, and a strong tendency to invasion and metastasis despite minimal or no invasion within the uterine cavity, leading to advanced stage, high recurrence rates, and a poor prognosis.

Endometrial cancers are staged surgically in accordance with the 2009 French Federation Internationale de Gynecologie et d'Obstetrique (FIGO) staging system (Table 2), which is a revision of the 1988 FIGO staging system.[4] Four major differences between the 1988 and 2009 FIGO staging systems for endometrial cancers are: (1) the 1988 FIGO IA and IB are combined into the 2009 FIGO IA, and the 1988 FIGO IC is now the 2009 FIGO IB; (2) Stage II no longer has subsets A and B, and endocervical glandular invasion is considered as Stage I; (3) positive cytology is no longer part of Stage III; and (4) pelvic and para-aortic lymph node invasion is classified as IIIC, based on the poor prognosis.[5]

The standard surgical staging treatment for endometrial cancer includes cytology, total hysterectomy, and bilateral salpingo-oophorectomy with/without the requirement of lymph node sampling and lymph node dissection, although some modifications are made for different populations based on differences in intent and conditions, such as fertility preservation and/or very earlier stage and well-differentiated endometrioid cancer.[3] In theory, oophorectomy might be beneficial in the management of endometrial cancer,[6] because oophorectomy can remove occult ovarian metastases and decrease estrogen production.[6]

In general, the majority of patients have FIGO Stage I endometrial cancer (72.6% at Taipei Veterans General Hospital) with a favorable 5-year outcome (98.7% and 90.5% for 2009 FIGO IA and IB, respectively).[4] However, the prognosis in advanced/recurrent disease is poor and presents a therapeutic challenge, even for those patients with Type I endometrial cancers. Many endometrial cancers express estrogen (ER) and/or progesterone (PR) receptors; consequently, there are numerous case reports, retrospective studies, and small Phase 2 studies that use a variety of hormonal therapies in patients with recurrent/metastatic endometrial cancers. The most commonly used agents are progestogens, tamoxifen, gonadotropin-releasing hormone agonist (GnRH agonist), and aromatase inhibitors (AIs). The following section highlights current knowledge on the use of hormonal therapy in recurrent endometrial cancer.

Table 1
The basic differences between Type I and Type II endometrial cancers.

	Type I	Type II
Incidence	≥80%	≤20%
Age	Varied	Postmenopause
Histology	Endometrioid	Serous, clear
Grade	Low	High
Clinical behavior	Less aggressive	More aggressive
Estrogen relation	Much evidence	Less evidence
BMI	High	Low
Parity	Low or null	Varied
Presence of precursor lesion	EIN or hyperplasia with/without atypia	Uncertain EIC
IHC	50–80% *PTEN* mutation	0–5% *PTEN* mutation
	14–20% p53 Mutation	90% p53 Mutation
	10–20% E-cadherin	80–90% E-cadherin
	20–45% MSI	0% MSI
	14–44% β-Catenin	0–5% β-Catenin
	10–18% Aneuploidy	85–95% Aneuploidy
	10–30% K-ras mutation	45–80% Her/neu overexpression P16 mutation
	Often with ER, PR, or AR positivity	

AR = androgen receptor; BMI = body mass index; EIC = endometrial intraepithelial carcinoma; EIN = endometrial intraepithelial neoplasia; ER = estrogen receptor; IHC = immunohistochemical staining; MSI = microsatellite instability; PR = progesterone receptor; *PTEN* = phosphatase and tensin homolog.

Table 2
Differences between the FIGO 1988 and FIGO 2009 staging systems of endometrial cancer.

Stage	FIGO 1988	FIGO 2009
I	*Confined to uterine corpus (invasion)*	
IA (1988, 2009)	Limited to endometrium	<1/2 myometrium
IB (1988, 2009)	<1/2 myometrium	≥1/2 myometrium
IC (1988)	≥1/2 myometrium	—
II (2009)	*Confined to cervix*	*Cervical stromal invasion, not extending beyond the uterus*
IIA (1988)	Endocervical gland	—
IIB (1988)	Cervical stroma	—
III (1988, 2009)	*Local and/or regional spread (invasion) of the tumor*	
IIIA (1988, 2009)	Serosa or adnexa or malignant cytology	Serosa and/or adnexa
IIIB (1988, 2009)	Vagina	Vagina and/or parametrium
IIIC (1988)	*Pelvic and/or para-aortic LN*	
IIIC1 (2009)	—	Pelvic LN
IIIC2 (2009)	—	Para-aortic LN
IV (1988, 2009)	*Bladder and/or bowel mucosa, and/or distant metastases*	
IVA (1988, 2009)	Bladder and bowel mucosa	
IVB (1988, 2009)	Distant metastases, including intra-abdominal metastases and/or inguinal LN	

Positive cytology has to be reported separately without changing the stage. Grading (G1, G2, G3) has to be reported separately without changing the stage.
FIGO = Federation Internationale de Gynecologie et d'Obstetrique; LN = lymph nodes.

3. Diagnosis of recurrent endometrial cancer

Before addressing the topic on the use of hormones in the management of recurrent endometrial cancer, clarifying the

issue of how to diagnose recurrent endometrial cancer is of paramount importance. The endometrial cancer recurrence rate ranges from 7.7% to 19%.[7] The majority of recurrences, ranging from 68% to 100%, were detected within 3 years, and the rate of symptomatic recurrence ranged from 70% to 77%.[8] Tests used routinely as part of follow-up programs are physical examination, vaginal vault cytology, chest X-ray, abdominal pelvic ultrasound, abdominal pelvic computed tomography, and CA 125. However, recurrences detected during these incidental tests ranged from 0% to 33%, suggesting that their use seems to be of low value and they should not be used without new evidence that can aid in making a decision on the most appropriate follow up for patients.[9] The diagnosis of endometrial cancer is often at an early stage, and primary treatment, often mediated through complete staging surgery, usually cures the majority of patients. In addition, postoperative adjuvant therapy, including radiation either in the form of vaginal vault brachytherapy, pelvic external beam radiation, or other modalities, may be arranged for patients at a higher risk for recurrence, such as Stage IA, Grade 3, Stage IC, or advanced stage.[7] This then raises questions, including: (1) what is an appropriate strategy for the follow up of these patients who are clinically disease-free? and (2) do differences in follow-up intervals, diagnostic interventions, clinical setting, or specialty influence patient outcomes related to local or distant recurrence, survival, or quality of life?[7] The anatomic locations of recurrences are roughly equivalent between the local pelvis and distant sites such as intra-abdominal regions and the lungs,[9] although data from one study showed two-fifths of patients with local recurrence and the three-fifths with distant metastases.[8] There is some controversy surrounding the salvage rate among recurrent patients, which ranged from 10% to 38%.[10,11] Treatment of recurrent disease depends on the original stage, location of the recurrence, and previous treatment.[12] The majority of isolated vaginal recurrences in women with surgical Stage I endometrial cancer can be successfully salvaged with radiation therapy, with a 5-year overall survival rate of nearly 75%.[12] The prognosis of patients with distant recurrence is generally not favorable, and these patients are often treated systemically, including chemotherapy and hormone therapy. Among these treatments, hormone therapy with progestins has been a favored option because of its minimal toxicity.[12]

4. Progesterones/progestins

Progesterone was discovered in 1933. Its effects are mediated through interaction with the PR, a transcription factor, and member of a large family of structurally related gene products known as the nuclear receptor superfamily.[13] Two isoforms of the PR, PRA and PRB, are generated by alternative transcription and translation from the same gene, because the amino acid sequences are identical and PRB has a longer N terminus (additional 164 amino acids). Both PRA and PRB are expressed in the normal endometrium and have distinct roles.[14] For example, alternation of PR isoform expression or loss of total PR leads to hyperplasia or even tumor formation.[13]

It is well known that estrogen-based hormonal therapy increases the incidence of endometrial hyperplasia and cancer, but the addition of a synthetic progestin (estrogen–progestin therapy) prevents the development of endometrial cancer and might decrease the incidence of the risk of endometrial cancer, suggesting that progesterone is an important inducer of endometrial differentiation and an inhibitor of carcinogenesis mediated through estrogen.[15,16]

In the early 1950s, endometrial cancers were treated with progestational agents, and the objective response rate was approximately 30%.[17] The advantages of hormones are that they are less toxic, less expensive, and easier to administer than parenteral chemotherapeutic agents, although chemotherapy is the standard antineoplastic treatment option for most women with advanced or recurrent endometrial cancers, based on the results of the Gynecologic Oncology Group (GOG) clinical trial 163.[18] The GOG 163 showed 34% and 57% objective response rates for these advanced or recurrent endometrial cancers when doxorubicin plus cisplatin without or with paclitaxel was used, respectively. The Cochrane analysis of 1519 patients found that treatment consisting of more chemotherapy was associated with longer overall survival and longer progression-free survival, even though serious acute toxicities were more common in women randomized to the more intense chemotherapy regimen.[19]

Frequently used regimens are medroxyprogesterone acetate (MPA; Depo-Provera), ranging from 200 to 500 mg/day, and megestrol acetate (MA; Megace), ranging from 40 to 320 mg/day. However, for those patients with recurrent endometrial cancer undergoing progestin therapy, high doses of MPA or MA seemed not to be superior to low doses of MPA or MA, because the efficacy did not increase, but the adverse effects, including edema, weight gain, and the risk of venous thromboembolism increased significantly (GOG 081).[20] In addition, the efficacy of progestin in the management of recurrent endometrial cancers was less effective (11–25%; GOG 081 and GOG 121),[21–24] compared with the original reports (30–56%).[18,25] Furthermore, the response in cases of recurrent endometrial cancer treated with progestins is often partial and the duration is often short (a median 3.2-month progression-free survival and a median 11.1-month overall survival in GOG 081),[21] although one report showed that some patients have a progression-free survival of more than 12 months.[26] The response rate of these recurrent endometrial cancers undergoing progestin treatment can be predicted by the presence of PR in tumors, because the response rate was 37% in patients with PR-positive tumors and 8% in patients with PR-negative tumors.[21]

5. Some modifications of progestins

With respect to hormone receptor status in GOG 081,[21] the hypothesis[27,28] that tamoxifen would prevent PR down-regulation, and therefore improve response, especially the

duration of response, thereby favorably impacting median progression-free and overall survival, was tested. An Eastern Cooperative Oncology Group Study (E4882) randomized patients to either the standard progestin therapy of MA (20% response rate: 1 complete and 3 partial among 20 patients) or the combination of MA and tamoxifen therapy (19% response rate: 1 complete and 7 partial among 42 patients) and concluded that the combination of MA and tamoxifen offers no clinical advantages over MA alone in the treatment of advanced endometrial cancer.[28] However, a Phase II study of MPA plus tamoxifen (GOG 119) showed a 33% response rate (6 complete and 13 partial among 58 patients) with a median 3-month progression-free survival and a median 13-month overall survival; therefore, the authors concluded that the combination of daily tamoxifen and intermittent weekly MPA is an active treatment for advanced or recurrent endometrial cancer.[29] Another Phase II study of an alternative course of MA and tamoxifen (GOG 153) showed a 27% response rate (12 complete and 3 partial among 56 patients), and up to 53% of the responders had a response duration of more than 20 months; therefore, the authors concluded that this regimen of alternating MA and tamoxifen is active in treating endometrial cancer and may result in a prolonged complete response in some patients.[30] Singh and colleagues further studied the relationship of ER and PR to clinical GOG 119 outcomes and concluded that ER-alpha measured in metastatic endometrial carcinoma tissue before hormonal therapy was statistically significantly related to clinical response to daily tamoxifen and intermittent MPA.[31] The aforementioned clinical trials are summarized in Table 3.[20–23,26,28–31,38,39]

However, a recent Cochrane review questioned the value of adjuvant progestagens for endometrial cancer, because a meta-analysis of 4556 patients failed to support its use in the primary treatment of endometrial cancer.[32] This suggested that further research and development of hormonal manipulation in endometrial cancer, such as epigenetic modulation, including methylation, histone acetylation, and others, is warranted.

6. Other hormones

The expression of ER in endometrial cancer provides a rationale for the use of tamoxifen or other selective ER modulators (SERMs).[33] SERMs are often used in the management of breast cancer in premenopausal women and osteoporosis in postmenopausal women, with selection, activation, and suppression of ER.[16,34–37] Tamoxifen has diverse effects in the pathogenesis of endometrial cancer because of its potential therapeutic effects on an established endometrial cancer and the potential risk of inducing the formation of endometrial cancer.[35] Thigpen and colleagues used tamoxifen 20 mg two times/day in the management of advanced or recurrent endometrial cancer, with an overall response rate of 10%, a 1.9-month median progression-free survival, and an 8.8-month medial overall survival.[38] Rendina and colleagues compared the effects of tamoxifen and MPA and showed 53.4% and 56.2% response rates, respectively, for the two.[39] Rendina et al also showed promising results with combined tamoxifen and MPA therapy, with 14 (60.8%) participants in the tamoxifen group and 15 (62.5%) in the MPA group responding to the combination therapy when they suffered a relapse of endometrial cancer, experiencing a 2.7-month median progression-free survival and 14-month overall survial.[39] Arzoxifene, a modification of raloxifene, has been studied in a small Phase II study that showed a 31% response rate in hormone-receptor-positive or well-differentiated endometrial cancer, with a median response of 13.9 months.[40]

GnRH agonist has been used in the management of various kinds of benign or malignant gynecological tumors.[41–43] It is mediated either through the direct effect of the GnRH–GnRH receptor pathway or through downregulation of the GnRH receptor, producing a subsequent suppression of ovarian function and decrease of estrogen levels. Studies in the UK evaluated the efficacy of GnRH agonists in the management of recurrent endometrial cancer.[44,45] An open Phase II observational trial showed a 35% response rate (6/17), with a median

Table 3
Trials of progestin or tamoxifen or combination in metastatic or recurrent endometrial cancer.

Authors (y)	Regimen	*n*	RR (%)	PFS (mo)	OS (mo)
Thigpen et al[20] (1999)	MPA 200 mg/day	145	25	3.2	11.1
	MPA 1000 mg/day	154	15	2.5	7.0
Lentz et al[21] (1996)	MA 800 mg/day	54	24	2.5	7.6
Piver et al[22] (1980)	Depo-Provera	114	15.8	NA	NA
Podratz et al[23] (1985)	Delalutin, Colprone, or MA	155	11.2	NA	12*
Carlson et al[26] (1984)	TAM	25	33	NA	NA
Pandya et al[28] (2001)	MA + tamoxifen	42	19	NA	12.0
Whitney et al[29] (2004)	TAM 40 mg/day plus alternating MPA 200 mg/week	58	33	3.0	13.0
Fiorica et al[30] (2004)	MA 80 mg b.i.d. × 3 weeks alternating with TAM 20 mg b.i.d. × 3 weeks	56	27	2.7	14.0
Singh et al[31] (2007)	TAM 40 mg/day plus alternating MPA 200 mg/week	58	33	—	—
Thigpen et al[38] (2001)	TAM 20 mg b.i.d.	68	10	1.9	8.8
Rendina et al[39] (1984)	TAM 20 mg b.i.d.	45	53.4	NA	NA
	MPA 1 g/wk intramuscularly	48	56.2	NA	NA

12* = 40% of patients survived more than 1 year; b.i.d. = two times daily; colprone = 6,17 alpha-dimethyl-6-dehydroprogesterone; delalutin = 17 alpha-hydroxyprogesterone caproate; MA = megestrol acetate; mo = months; MPA = medroxyprogesterone acetate; *n* = number of patients; NA = no data available; OS = overall survival; PFS = progression-free survival; RR = response rate; TAM = tamoxifen; wk = week; y = year of publication.

of 20 months with no adverse effects.[44] Five years later, the same group reported that the response rate was 28% in 32 patients with recurrent endometrial cancer.[45] The significantly greater response rates were in previously irradiated sites, compared with nonirradiated sites of recurrence, suggesting that GnRH agonists have a significant and durable antitumor effect in recurrent endometrial cancer.[45] A GOG trial evaluated the effect of GnRH agonist in patients with advanced and recurrent endometrial cancer, and found an 11% response rate (2 complete, 3 partial among 42 patients), with a 1.9-month median progression-free survival and 7.3-month median overall survival.[46]

AIs block the aromatase enzyme, resulting in reduced estrogen levels and deprive the tumor of growth stimulation.[47] A GOG Phase II trial evaluated the effect of AIs in patients with advanced or recurrent endometrial cancer and found a 9% response rate (2 partial, 2 stable among 23 patients).[47] Although the toxicity profile was mild, anastrozole, an AI, had only minimal activity in an unselected population of patients with recurrent endometrial cancer.[47] A multicenter Phase II trial conducted by the National Cancer Institute of Canada Clinical Trials Group further showed the low response rate (9.4%, 1 complete, 2 partial among 28 patients) of letrozole (another AI) in the management of patients with advanced or recurrent endometrial cancer.[47] However, 11 patients (39%) had stable disease for a median duration of 6.7 months, suggesting that letrozole is well tolerated but has little overall activity in patients with advanced or recurrent endometrial cancer.[48] Table 4[40,44−48] shows the summary of these trials.

In conclusion, primary advanced or recurrent endometrial cancer remains an entity with a dismal outcome and with less than optimal therapeutic options. Patients with metastatic disease are not curable and should be considered for palliative chemotherapy. Some data support the use of carboplatin and paclitaxel as an acceptable alternative to cisplatin-based regimens; however, the options are limited when those patients progress after first-line treatment.[49] In these situations, hormone therapy, especially progestins with/without tamoxifen, although response rate is not satisfactory, remains a valid option for some patients with favorable histologic and molecular characteristics, because a cure is impossible and toxicity is a major concern. With much more advanced molecular development, new avenues of treatment may enhance the effectiveness of hormone therapy for endometrial cancer.

Table 4
Trials of other hormone regimens in metastatic or recurrent endometrial cancer, excluding tamoxifen, megestrol acetate (Megace), or medroxyprogesterone.

Authors (y)	Regimen	*n*	RR (%)	PFS (mo)	OS (mo)
McMeekin et al[40] (2003)	Arzoxifene 20 mg	34	31	13.9	NA
Gallagher et al[44] (1991)	GnRH agonist	17	35	NA	20
Jeyarajah et al[45] (1996)	GnRH agonist	32	28	NA	34
Asbury et al[46] (2002)	GnRH agonist	40	11	1.9	7.3
Rose et al[47] (2000)	Anastrozole	23	9	1.0	6.0
Ma et al[48] (2004)	Letrozole 2 mg	28	9.4	6.7	NA

GnRH agonist = gonadotropin-releasing hormone agonist; mo = months; *n* = number of patients; OS = overall survival; PFS = progression-free survival; RR = response rate; y = year of publication.

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