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E23. Endocrine therapy for metastatic endometrial cancer

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In the past decades, progestogens have been the 'cornerstone' of treatment for metastatic endometrial cancer. The oestrogen receptor (ER) and progesterone receptor (PR) levels are related to the stage, grade and prognosis of the disease. The response to progestogens is related to the PR-status (Table 1). However, progestogens have no proven effect in the adjuvant setting [1].

The optimal dose of progestogen has been debated. In a Gynaecologic Oncology Group (GOG)-trial, randomising 299 patients with metastatic endometrial cancer, it was shown that 200 mg of Medroxyprogesterone Acetate (MPA) was as effective as 1000 mg MPA daily [10]. Based on this trial, a daily dose of 200 mg MPA is recommended for the treatment of recurrent or metastatic endometrial cancer.

Adjuvant tamoxifen treatment increases the risk of endometrial carcinoma in breast cancer patients, with a hazard ratio of 2.5 being reported [11]. Despite this, tamoxifen has also been shown to be active in advanced or recurrent endometrial cancer, resulting in response rates of 29% (Table 2). When tamoxifen is combined with progestogens the response rates did not improve [20–22].

Raloxifene, another selective oestrogen receptor modulator (SERM), is not associated with an increased risk of endometrial cancer [23]. A newer SERM, arzoxifene, has also been investigated by McMeekin and colleague [24], and the response rate in 34 patients treated with 20 mg was 31%. However, all these patients were progestagen-sensitive. In a more recent European study, 66 patients with recurrent or metastatic endometrial cancer were treated with arzoxifene. In this study, the overall response rate was 25% (34% in progestagen-sensitive patients). As with other SERMS, a possible relationship between arzoxifene and an increased risk of pulmonary embolisms was observed.

The newer third generation aromatase inhibitors have also been explored as treatments for endometrial cancer. In a GOG phase II study 1 mg of anastrozole was given to 23 patients. Only 2 of 23 patients had a partial remission (both were progestagen-sensitive) [25]. Other third generation aromatase inhibitors, letrozole and exemestane, are presently under investigation.

Danozole, interferes with the function of the pituitary gonadotropins and is an inhibitor of ovarian

Table 1
Progesterone Receptor and response to progestagens in endometrial cancer

Authors (year) [Ref.]	PR-negative		PR-Positive	
	Responders	Total	Responders	Total
Martin (1979) [2]	1	6	13	14
McCarthy (1979) [3]	0	8	4	5
Benraad (1980) [4]	2	7	5	6
Creasman (1980) [5]	1	8	3	5
Kauppila (1982) [6]	1	17	2	4
Pollow (1983) [7]	0	13	9	9
Quinn (1985) [8]	0	13	3	10
Ehrlich(1988) [9]	6	34	6	10
Total	11 (10%)	106	45 (71%)	63

PR, progesterone receptor.

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Table 2
Tamoxifen in advanced or recurrent endometrial cancer

Author (year) [Ref.]	Previous progestagen	Responders	Total
Swenerton (1979) [12]	Yes	4	7
Bonte (1981) [13]	Yes	10	17
Kauppila (1981) [14]	Yes	1	1
Hald (1983) [15]	Yes	2	9
	No	6	17
Rendina (1984) [16]	No	24	45
Slavik (1984) [17]	Yes	0	24
Edmonson (1986) [18]	Yes	0	22
	No	5	24
Quinn (1989) [19]	Yes	10	49
Total	Yes or no	62 (29%)	215
	Yes	27 (21%)	129
	No	35 (41%)	86

steroidogenesis, reversing endometrial hyperplasia in 97% of patients [26]. However, this drug produced no responses in a GOG phase II study in recurrent endometrial cancer patients (N=22) [27]. Disappointing results were also obtained using Gonadotrophin-releasing hormone (GnRH)-agonists [28].

Fulvestrant is a new type of ER antagonist that downregulates cellular levels of the ER. Fulvestrant inhibits oestrogen-stimulated thickening of the endometrium [29]. This compound merits further investigation in the treatment of metastatic endometrial cancer.

References

1. Vergote I, Kjorstad K, Abeler V, Kolstad P. Randomized trial of adjuvant progesterone in early endometrial cancer. *Cancer* 1989, **64,** 1011–1016.
2. Martin PM, Rolland PH, Gammerre M, Serment H., Toga M. Estradiol and progesterone receptors in normal and neoplastic endometrium: correlation between receptor, histopathological examinations and clinical response under progestin therapy. *Int J Cancer* 1979, **23**, 321–329.
3. McCarthy KS Jr., Barton TK, Fetter BF, Creasman WT, McCarthy KS Sr. Correlation of oestrogen and progesterone receptors with histological differentiation in endometrial carcinoma. *Am J Pathol* 1979, **96**, 171–182.
4. Benraad TJ, Friberg LG, Koenders AJM, Kullander S. Do oestrogen and progesterone receptors (E2R and PR) in metastasizing endometrial cancers predict the response to progestagen therapy. *Acta Obstet Gynecol Scand* 1980, **59**, 155–159.
5. CreasmanWT, McCarthy KS Sr, Barton TK, McCarthy KS Jr. Clinical correlates of oestrogen- and progesterone-binding proteins in human endometrial carcinoma. *Obstet Gynecol* 1980, **55**, 363–370.
6. Kauppila A, Isotalo H, Kujansuu E, Vihko R. Clinical significance of female steroid hormone receptors in endometrial carcinoma treated with conventional methods and medroxyprogesterone acetate. In: Carelli F, *et al.* editors. *International symposium on medroxyprogesterone acetate. Excerpta medica international congress series No.* 611. Amsterdam: Excerpta Medica; 1982, p. 350–359.
7. Pollow K, Manz B, Grill JH. Estrorgen and progesterone receptors in endometrial cancer. In: Jasonni VM, editor. *Steroids and endometrial cancer*. New York: Raven Press; 1983, p. 33–60.
8. Quinn MA, Cauchi M, Fortune D. Endometrial carcinoma: steroid receptors and response to medroxyprogesterone acetate. *Gynecol Oncol* 1985, **21**, 314–319.
9. Ehrlich CE, Young PC, Stehman FB, Sutton GP, Alford WM. Steroid receptors and clinical outcome in patients with adenocarcinoma of the endometrium. *Am J Obstet Gynecol* 1988, **158**, 796–807.
10. Thipgen JT, Brady MF, Alvarez RD, Adelson MD, Homesley HD, Manetta A, *et al.* Oral Medroxyprogesterone Acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. *J Clin Oncol* 1999, **17**, 1736–1744.
11. Vergote I, Neven P, Vanderrick G, Van Dam P, Van Belle Y, De Sutter Ph, *et al.* Tamoxifen and the Uterus. *Eur J Cancer* 1998, **34**(Suppl 4), S1–S3.
12. Swenerton KD, Shaw D, White GW, Boyes DA. Treatment of advanced endometrial carcinoma with tamoxifen. *New Engl J Med* 1979, **301**, 105.
13. Bonte J, Ide P, Billiet G, Wynants P. Tamoxifen as a possible chemotherapeutic agent in endometrial adenocarcinoma. *Gynecol Oncol* 1981, **11**, 140–161.
14. Kauppila A, Vihko R. Endometrial carcinoma insensitive to progestin and cytotoxic chemotherapy may respond to tamoxifen. *Acta Obstet Gynecol Scand* 1981, **60**, 589–590.
15. Hald I, Salimtschik M, Mouridsen HT. Tamoxifen treatment of advanced endometrial carcinoma: a phase II study. *Eur J Gynecol Oncol* 1983, **4**, 83–87.
16. Rendina GM, Donadio C, Fabri M, Mazzonni P, Nazzicone P. Tamoxifen and medroxyprogesterone therapy for advanced endometrial carcinoma. *Eur J Obstet Reprod Biol* 1984, **17**, 285–291.
17. Slavik M, Petty WM, Blessing JA, Creasman WT, Homesley HD. Phase II clinical study of tamoxifen in advanced endometrial adenocarcinoma: a Gynecologic Oncology Group study. *Cancer Treat Rep* 1984, **68,** 809–811.
18. Edmonson JH, Krook JE, Hilton JF, *et al.* Ineffectiveness of tamoxifen in advanced endometrial carcinoma after failure of progestin treatment. *Cancer Treat Rep* 1986, **70**, 1019–1020.
19. Quinn MA, Campbell JJ. Tamoxifen therapy in advanced/recurrent endometrial carcinoma**.** *Gynecol Oncol* 1989, **32**, 1–3.
20. Carlson JA, Allerga JC, Day TG Jr, Wittliff JL. Tamoxifen and endometrial carcinoma: alterations in oestrogen and progesterone

receptors in untreated patients and combination hormonal therapy in advanced neoplasia. *Am J Obstet Gynecol* 1984, **149**, 149–153.
21. Kline R, Freedman RS, Jones LA, Atkinson EN. Treatment of recurrent or metastatic poorly differentiated adenocarcinoma of the endometrium with tamoxifen and medroxyprogesterone acetate. *Cancer Treat Rep* 1987, **71**, 327–328.
22. Pandya KJ, Yeap BY, Weiner LM, Krook JE, Erban JK, Schinella RA, *et al*. Megestrol and tamoxifen in patients with advanced endometrial cancer. *Am J Clin Oncol* 2001, **24**, 43–46.
23. Cauley JA, Norton L, Lippman ME, Eckert S, Krueger KA, Purdie DW, *et al*. Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4 year results from the MORE trial. Multiple outcomes of raloxifene evaluation. *Breast Cancer Res Treat* 2001, **65**, 125–134.
24. McMeekin DS, Gordon A, Fowler J, Melemed A, Buller R, Burke T, *et al*. A phase II trial of arzoxifene, a selective oestrogen response modulator in patients with recurrent or advanced endometrial cancer. *Gynecol Oncol* 2003, **90**, 64–69.
25. Rose PG, Brunetto VL, VanLe L, Bell J, Walker JL, Lee RB. A phase II trial of Anastrozole in advanced recurrent or persistent endometrial carcinoma: a Gynaecologic Oncology Group Study. *Gynecol Oncol* 2000, **78**, 212–216.
26. Soh E, Sato K. Clinical effects of danazol on endometrial hyperplasia in menopausal and postmenopausal women. *Cancer* 1990, **66**, 983–988.
27. Covens A, Brunetto VL, Markman M, Orr JW, Lentz SS, Benda J. Phase II trial of danazol in advanced, recurrent, or persistent endometrial cancer: a Gynecologic Oncology Group Study. *Gynecol Oncol* 2003, **89**, 470–474.
28. Elit L, Hirte H. Current status and future innovations of hormonal agents, chemotherapy and investigational agents in endometrial cancer. *Curr Opin Obstet Gynecol* 2002, **14**, 67–73.
29. Addo S, Yates RA, Laight A. A phase I trial to assess the pharmacology of the new oestrogen receptor antagonist fulvestrant on the endometrium in healthy postmenopausal volunteers. *Br J Cancer* 2002, **87**, 1354–1359.