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Hormonal therapy for cancer

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Abstract

Hormone therapy is an effective and non-toxic therapy for oestrogen and progesterone receptor-positive breast cancer and for prostate cancer. Serum ~~levels~~ concentrations of oestradiol and testosterone are controlled by the hypothalamic–pituitary–gonadal pathway. Oestradiol is produced in premenopausal women from the ovaries, and in postmenopausal women by peripheral conversion of adrenal androgens by aromatase. In premenopausal women with breast cancer and men with prostate cancer, treatment is primarily achieved by castration. In postmenopausal women, selective oestrogen receptor modulators (e.g. tamoxifen) or aromatase inhibitors are used. Hormone therapy can be used to reduce the size of the primary cancer ~~before prior to~~ radical surgery or radiotherapy, or to reduce the risk of recurrence. Hormone therapy is highly effective in patients with locally advanced or metastatic disease, with high response rates. Most patients eventually relapse with hormone-refractory disease and ~~may can~~ be offered novel hormonal agents, chemotherapy or molecularly targeted agents.

Keywords

Androgen deprivation therapy; androgen receptor; antiandrogens; aromatase inhibitors; breast cancer; hormone therapy; prostate cancer; selective oestrogen receptor modulators

Key points

- Breast cancer is highly sensitive to hormonal therapies, with response rates related to oestrogen receptor and progesterone receptor status
- Recurrence is managed with a switch to other hormonal agents or addition of novel pathway inhibitors, which ~~has an improve~~ sd efficacy in metastatic breast cancer
- ~~Metastatic p~~Prostate cancer has an almost 100% response rate to initial androgen deprivation therapy (medical castration). ~~Relapse is , but relapse is inevitable and managed with addition , when patients are switched to of~~ more active hormonal agents or chemotherapy
- ~~Mechanisms Of~~ Resistance to these newer agents in prostate cancer ~~are is~~ emerging and should ~~lead to stimulate~~ further therapeutic approaches and improvements in outcome
- Patients can be on hormonal therapy for many years and awareness, prevention and management of late effects is critical

Background ~~(see also Breast Cancer on pages 42–46 and Prostate Cancer on pages 47–51 of this issue)~~

This paper ~~will~~ concentrates on the management of breast and prostate cancers in which the impact of hormone therapy is most clinically significant ~~(see also Breast Cancer on pages xx–xx and Prostate Cancer on pages xx–xx of this issue)~~. Increased exposure to endogenous or exogenous oestrogens ~~may may~~ be linked to the development of breast cancer (Table 1). However, there is no evidence that exposure to androgens is important in the development of prostate cancer.

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In 1896 Beatson demonstrated that surgical oophorectomy resulted in tumour regression in premenopausal women with metastatic breast cancer. Charles Huggins was awarded the Nobel Prize for medicine in 1966 [after](#) his discovery that surgical orchiectomy was a successful treatment for metastatic prostate cancer.

Hormone synthesis

Oestrogen is synthesized from cholesterol in the parafollicular ovaries in premenopausal women via the hypothalamic-pituitary-gonadal axis (Figure 1), and in the adrenals in postmenopausal women. In premenopausal women, oestrogen production is cyclical: gonadotrophin-releasing hormone (GnRH) is released from the hypothalamus with a circadian rhythm under direct feedback [from](#) circulating hormones. GnRH reacts with anterior pituitary receptors, leading to the release of luteinizing [hormone](#) (LH) and follicle-stimulating hormone (FSH); these stimulate the ovaries to produce oestradiol.

In postmenopausal women, the main site of oestrogen synthesis is adipose tissue. Here, adrenal androgens (e.g. androstenedione) are converted by aromatase to oestrone. Oestrone is then converted to oestradiol by 17 β -OH dehydrogenase. Postmenopausal synthesis varies depending on environmental and genetic factors (e.g. obesity).

In men, the main circulating androgen is testosterone, 90% of which is produced by the testicular Leydig cells under control of the hypothalamic-pituitary axis, as above. The remaining circulating androgens (e.g. dihydroxyandrostenedione) are produced in the adrenal cortex and the prostate itself from cholesterol. Testosterone is metabolized by 5 α -reductase within the prostate to the more biologically active dihydrotestosterone, which acts as the ligand for the androgen receptor (AR).

Hormone receptors

In breast cancer, approximately 80% of postmenopausal women and 50% of premenopausal women have hormone receptor-positive disease. The degree of positivity is defined by the level of expression of both oestrogen (ER) and progesterone receptors, which are routinely measured immunohistochemically in newly diagnosed [women](#). Systemic treatment and, to some extent, prognosis is guided by hormone receptor status.¹

In contrast, measurement of ARs is not currently routinely performed in prostate cancer as there is no or prognostic therapeutic value. However, recent work has shown that AR variants (e.g. ARv7) underlie resistance to castration, predict response to alternative AR-targeting agents and can be detected in both tumour tissue and circulating tumour cells.

Hormone therapy in breast cancer

Ovarian ablation

In premenopausal women, oestrogen suppression is achieved by chemical ablation, radiation to the ovaries or surgical oophorectomy. Chemical ablation is reversible and achieved using a GnRH (or LH-releasing hormone (LHRH)) agonist (GnRHa, LHRHa) such as goserelin or leuporelin, usually as a monthly depot injection.

Other hormonal agents in breast cancer

An increasing number of hormonal treatment options are available to treat breast cancer. A description of the different [drugs](#) [licensed in the UK](#) is given in Table 2. The most commonly used treatments include tamoxifen and aromatase inhibitors (AIs).

Tamoxifen: this is a selective oestrogen receptor modulator with complex actions on ERs, acting predominantly as an antagonist, with weak agonist effects. In ER-positive early breast cancer, 5 years of tamoxifen after surgery reduces the annual recurrence rate by 41% and annual mortality rate by 34%.² There is evidence of a reduction in breast cancer recurrence and mortality by continuing tamoxifen in ER-positive disease for 10 years rather than stopping at 5 years. Tamoxifen [can](#) be used in premenopausal and postmenopausal women. The main adverse effects are hot flushes, night sweats and vaginal discharge. There is an increased risk of thrombotic events. Vaginal bleeding should be promptly evaluated because of the increased risk of endometrial cancer.

Aromatase inhibitors: several Phase III clinical trials have established third-generation AIs as the new gold standard in the adjuvant hormonal treatment of receptor-positive early breast cancer. They are

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contraindicated in premenopausal women unless ovarian suppression has been induced. There are three main approaches with early breast cancer:

- up-front use for 5 years
- planned or unplanned switching, i.e. use of AIs for 2–3 years after 2–3 years of tamoxifen
- extended therapy, i.e. after 5 years' use of tamoxifen.

The main toxicities of AIs are hot flushes, arthralgia, reduced bone mineral density and increased risk of fractures. Women at risk of osteoporosis should be carefully monitored or treated with bisphosphonates where necessary.³ A new approach in treating metastatic disease is the use of AIs in combination with pathway inhibitors such as cyclin-dependent kinases (CDKs). CDK4/6 inhibitors such as palbociclib, ribociclib and abemaciclib used in combination with letrozole or fulvestrant have shown an improvement in progression-free survival and have become the treatment of choice providing the increased toxicity is manageable.

Main indications for hormonal therapy in breast cancer

- As a neoadjuvant to reduce the size of the primary tumour, making it operable or reducing the extent of surgery, for example from mastectomy to wide local excision.
- As an adjuvant after surgery to reduce the risk of recurrence and improve survival.
- As a palliative treatment to shrink and control large inoperable cancers.
- As a palliative treatment for metastatic disease to prolong and improve quality of life.

Hormone therapy in prostate cancer

Androgen deprivation therapy

Serum testosterone is reduced to castrate concentrations by surgical or chemical castration, with an LHRHa or the newer LHRH antagonists. Castration can lead to hot flushes, sweats and reduced libido. Patients can notice reduced muscle mass, reduced strength and weight gain. There can be loss of bone mineral density and there are concerns of an increased risk of fatal cardiac events.

Initial use of LHRHa results in a surge in serum testosterone, which can worsen symptoms: all patients should take oral antiandrogens for at least 3 weeks, starting 1–2 weeks before the initial LHRHa injection. Degarelix is an LHRH antagonist that rapidly achieves castrate concentrations of testosterone without a testosterone flare. It should be used in emergency situations such as new diagnoses presenting with metastatic spinal cord compression or renal tract obstruction.

Hormonal therapy is not curative and metastatic patients inevitably relapse at some stage; this is termed 'castrate-refractory prostate cancer' (CRPC).

Other hormonal agents in prostate cancer

The key agents used in the management of prostate cancer are described in Table 3.

Bicalutamide is a non-steroidal antiandrogen and competitive AR inhibitor. It can be used as an alternative to an LHRHa, with a lower incidence of erectile dysfunction, but equivalent efficacy has not been proven. It can be added to an LHRHa as a low-toxicity agent for CRPC, with a response rate up to 66%.

Abiraterone acetate, enzalutamide, apalutamide and darolutamide are newer agents providing much greater AR suppression. Trials have shown prolongation of overall survival in combination with androgen deprivation therapy in hormone-sensitive metastatic prostate cancer, such that median survival is now ≥5 years. There is also evidence improved progression-free and/or overall survival in both non-metastatic and metastatic CRPC.^{4,5} Abiraterone is an androgen synthesis inhibitor blocking adrenal and prostatic production of androgens. Enzalutamide, apalutamide and darolutamide are potent AR inhibitors that also block the translocation of activated AR to the nucleus and interactions between AR and DNA.

Corticosteroids are highly active in CRPC but have no proven survival advantage and are not licensed in the UK for use in prostate cancer. Long-term use is associated with typical glucocorticoid adverse effects, such as proximal myopathy and reduced bone mineral density, and patients require regular review.³

Main indications for hormonal treatment in prostate cancer

- Neoadjuvant therapy before radiotherapy to improve local and biochemical (prostate-specific antigen) control in patients with locally advanced tumours.

- As an adjuvant [after](#) radiotherapy to improve overall survival in high-risk disease.
- Palliatively for metastatic hormone-sensitive and [CRPC](#). Almost [all](#) patients respond to initial hormonal therapy, with a median [response](#) duration of 12 months.⁴ Response rates to further hormonal manipulation with novel agents is approximately 80% for CRPC.⁵

Hormone resistance

Resistance develops in nearly all patients with metastatic breast and prostate cancer who initially respond to hormone therapy, resulting in disease progression. The molecular causes of resistance are complex, varied and not well understood. Mechanisms [may](#) include increased sensitivity of hormone receptors, hormone receptor variants, pathway activation without exposure to hormones (constitutive activation) or upregulated downstream survival pathways. As these become better characterized, new agents are being developed, trialled and introduced into practice.

Hormonal risks for breast cancer

Risk factors	Protective factors
Early menarche	Breastfeeding
Late menopause	Young age at full-term pregnancy
Nulliparity	
Obesity	
Hormone replacement therapy	

Table 1

Key hormonal therapies in breast cancer

Drug	Type	Dose/route	Mode of action
Tamoxifen	Anti-oestrogen	20 mg daily p.o.	Competes with oestradiol for ER binding
Anastrozole	Non-steroidal aromatase inhibitor	1 mg daily p.o.	Competitive aromatase inhibition
Letrozole	Non-steroidal aromatase inhibitor	2.5 mg daily p.o.	Competitive aromatase inhibition
Exemestane	Steroidal aromatase inhibitor	25 mg daily p.o.	Irreversible aromatase inhibition
Fulvestrant	Oestrogen receptor ER antagonist	250 mg monthly deep i.m.	Down-regulation of the ER protein
Megestrol acetate	Progestin	80 –160 mg daily p.o. <u>in single or divided doses</u>	Cellular action not fully understood Down-regulation of ovarian steroidogenesis

ER, oestrogen receptor; i.m., intramuscular; p.o., oral.

Table 2

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Key hormonal therapies in prostate cancer

Drug	Type	Dose/route	Mode of action
Goserelin	LHRH a -agonist	3.6 mg every 28 days or 10.8 mg every 3-12 weeks ^{months} s.c.	Reduced pituitary production of LH and FSH
Leuprorelin	LHRH a -agonist	3.75 mg every 28 days s.c. or i.m. or 11.25 mg every 3-3 months ^{months} — s.c./ i.m.	Reduced pituitary production of LH and FSH
Degarelix	LHRH antagonist	240 mg then 80 mg every 28 days s.c.	Reduced pituitary production of LH and FSH
Bicalutamide	Non-steroidal antiandrogen	50 mg (combination dose) or 150 mg (single agent) daily p.o.	Competitive AR inhibition
Prednisolone (unlicensed)	Corticosteroid	5–10 mg daily p.o.	Adrenal suppression
Dexamethasone (unlicensed)	Corticosteroid	0.5–2 mg daily p.o.	Adrenal suppression
Abiraterone acetate	Androgen synthesis inhibitor	1000 mg daily p.o. (with prednisolone 5 mg twice-once or twice daily p.o.)	Reduced androgen production within adrenal glands and prostate cancer cells
Enzalutamide	AR inhibitor	160 mg daily p.o.	Competitive AR inhibition, block of AR translocation to the nucleus
Apalutamide	AR inhibitor	24 60 mg daily p.o.	Competitive AR inhibition, block of AR translocation to the nucleus

AR, androgen receptor; FSH, follicle-stimulating hormone; i.m., intramuscular; LH, luteinizing hormone; LHRH, luteinizing hormone-releasing hormone; p.o., oral; s.c., subcutaneous.

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Table 3

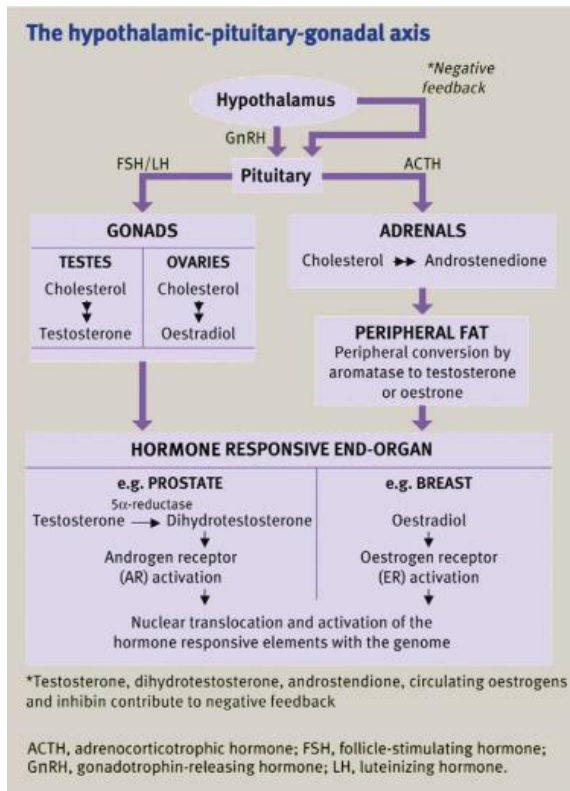


Figure 1

KEY REFERENCES

- 1 Early Breast Cancer Trialists' Collaborative Group (EBCTC G). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; **365**: 1687–717.
- 2 Davies C, Pan H, Godwin J, et al. Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group. Long term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor positive breast cancer: ATLAS, a randomised trial. *Lancet* 2012; **381**: 805–16.
- 3 Royal College of Physicians, Bone and Tooth Society, National Osteoporosis Society. Glucocorticoid-induced osteoporosis: guidelines for prevention and treatment. London: RCP, 2002.
- 4 Davis ID, Martin AJ, Stockler MR, et al. ENZAMET Investigators. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *New Engl J Med* 2019; **381**: 121–31.
- 5 Fizazi K, Scher HI, Molina A, et al. COU-AA-301 Investigators. Abiraterone acetate for treatment of metastatic castration resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol* 2012; **13**: 983–92.

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online [here](#).

Question 1

A 62-year-old man presented acutely with urinary retention, thoracic back pain and decreased mobility. On clinical examination, there was a suprapubic mass, a hard irregular prostate and decreased power in the lower limbs.

Investigations

- Prostatic specific antigen 160 microgram/litre (<4)
- Plain X-rays of the back showed multiple sclerotic lesions throughout the thoracic spine
- MR scanning of the spine showed metastatic spinal cord compression at multiple levels including T5

What is the most appropriate hormonal therapy to use, in addition to the standard management of

- A Start single-agent bicalutamide 150 mg daily
- B Start bicalutamide 50 mg daily and give goserelin 3.6 mg s.c. in a week's time
- C Start degarelix 240 mg s.c. and give a further injection of 80 mg in 4 weeks' time
- D Start bicalutamide 50 mg o.d. and give goserelin 3.6 mg s.c. immediately
- E Start degarelix 240 mg s.c. and add abiraterone 1000 mg o.d. with prednisolone 5 mg daily in a week's time

Correct answer: C. Degarelix

Question 2

A 65-year-old woman presented with a lump in the right breast. Examination and investigations confirmed this as a carcinoma with a high level of expression of both oestrogen and progesterone receptors. The tumour was large and in a small breast and, to avoid a mastectomy, the decision was taken to reduce the size by systemic therapy prior to surgery with a wide local excision.

What is an appropriate therapeutic hormonal intervention to achieve this?

- A Gonadotrophin-releasing hormone agonists
- B Chemotherapy
- C Aromatase inhibitors
- D Progesterone receptor antagonists
- E A selective oestrogen receptor modulator

Correct answer: E. Aromatase inhibitors (C) is the most appropriate agent to use in this situation and

Commented [JC11]: AQ: I've tried here to get to the basic mechanisms rather than the specific drugs, which may soon go out of date. Needs expert review as it's well outside my field and feedback added if it's satisfactory.
Goserelin is given as an GnRH agonist but I understand its later therapeutic action is an antagonist. I'm not sure the text makes that clear.