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 prostate cancer. Serum levels 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 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 a high response rate. Most patients eventually relapse with ‘castrate-refractory’ disease, for which increasing numbers of active agents are entering clinical practice.

Keywords: Androgen deprivation therapy; anti-androgens; aromatase inhibitors; breast cancer; hormone therapy; prostate cancer; selective oestrogen receptor modulators

Aetiology

This paper will concentrate on the management of breast and prostate cancers in which the impact of hormone therapy is most clinically significant. Increased exposure to endogenous or exogenous oestrogens 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.

Historical evidence

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 following his discovery that surgical orchidectomy 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 by circulating hormones. GnRH reacts with anterior pituitary receptors, leading to the release of luteinizing and follicle-stimulating hormone; these stimulate the ovaries to produce oestriadiol.

In postmenopausal women, the main site of oestrogen synthesis is adipose tissue. Here, adrenal androgens (e.g. androstenedione) are converted from aromatase to oestrone. Oestrone is then converted to oestradiol by 17β-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 from cholesterol. Testosterone is metabolized by 5α-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 cases. Systemic treatment and, to some extent, prognosis is guided by hormone receptor status.

In contrast, measurement of ARs is not currently routinely performed in prostate cancer – it has no therapeutic or prognostic value because both hormone-dependent and ‘castrate-refractory’ prostate cancers (CRPCs) possess functioning ARs. Recent work suggests that AR variants may underlie resistance to castration.1

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 by using a GnRH agonist (GnRHa or LHRHa) such as goserelin, 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 licensed drugs 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 a 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.3 Tamoxifen may 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.4
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 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.5

A new approach is the use of AIs in combination with signal transduction or pathway inhibitors. Everolimus is an mTOR inhibitor licensed for use in combination with exemestane in the metastatic setting.6

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 (ADT)

Serum testosterone is reduced to castrate levels by surgical or chemical castration, using LHRHa or the newer LHRH antagonists. Castration can lead to hot flushes, sweats and reduced libido. Patients may 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 may worsen symptoms: all patients should take oral antiandrogens for at least 3 weeks, starting 1–2 weeks prior to initial LHRHa injection. This is not needed with LHRH antagonists, which are preferred in emergency situations.

Other hormonal agents in prostate cancer

The hormonal agents commonly used in the management of CRPC are described in Table 3.

Bicalutamide is a non-steroidal antiandrogen and competitive AR inhibitor that is often used as the initial agent for CRPC, with a response rate up to 66%. Single-agent bicalutamide (at a dose of 150 mg daily) can be used as an alternative to ADT in some clinical situations. There is a lower incidence of erectile dysfunction but equivalent efficacy has not been proven.

Degarelix is an LHRH antagonist and does not cause a testosterone flare. It rapidly achieves castrate levels of testosterone and can be used in emergency situations such as new diagnoses presenting with cord compression.

Abiraterone acetate and enzalutamide are newer agents causing much greater AR suppression, through different mechanisms; they have been shown to prolong survival both before and after docetaxel chemotherapy.7–10
Corticosteroids are highly active in CRPC but have no proven survival advantage. Long-term use is associated with typical glucocorticoid adverse effects, such as proximal myopathy and reduced bone mineral density, and patients require regular review.

**Main indications for hormonal treatment in prostate cancer**

- As a neoadjuvant prior to radiotherapy to improve local and biochemical (prostate-specific antigen) control in patients with locally advanced tumours
- As an adjuvant following radiotherapy to improve overall survival in high-risk disease
- Palliatively for metastatic or recurrent prostate cancer. Almost 100% of patients respond, with a median duration of response of 12 months.

**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, pathway activation without exposure to hormones (constitutive activation) or up-regulated downstream survival pathways. As these become better characterized, new agents can be developed and trialled.
<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Protective factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early menarche</td>
<td>Breast-feeding</td>
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<tr>
<td>Late menopause</td>
<td>Young age at full-term pregnancy</td>
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<tr>
<td>Nulliparity</td>
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<tr>
<td>Obesity</td>
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<tr>
<td>Hormone replacement therapy</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Type</td>
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<tr>
<td>---------------</td>
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</tr>
<tr>
<td>Tamoxifen</td>
<td>Anti-oestrogen</td>
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<tr>
<td>Anastrozole</td>
<td>Non-steroidal aromatase inhibitor</td>
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<tr>
<td>Letrozole</td>
<td>Non-steroidal aromatase inhibitor</td>
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<tr>
<td>Exemestane</td>
<td>Steroidal aromatase inhibitor</td>
</tr>
<tr>
<td>Fulvestrant</td>
<td>Oestrogen receptor antagonist</td>
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<tr>
<td>Megestrol acetate</td>
<td>Progestin</td>
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</tbody>
</table>

ER, oestrogen receptor; i.m., intramuscular; p.o., oral.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Type</th>
<th>Dose/route</th>
<th>Mode of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goserelin</td>
<td>LHRH agonist</td>
<td>3.6 mg every 28 days or 10.8 mg every 3 months s.c.</td>
<td>Reduced pituitary production of LH and FSH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.75 mg every 28 days or 11.25 mg every 3 months s.c./i.m.</td>
<td>Reduced pituitary production of LH and FSH</td>
</tr>
<tr>
<td>Leuprorelin</td>
<td>LHRH agonist</td>
<td>240 mg then 80 mg every 28 days s.c.</td>
<td>Reduced pituitary production of LH and FSH</td>
</tr>
<tr>
<td>Degarelix</td>
<td>LHRH antagonist</td>
<td>50 mg (combination dose) or 150 mg (single agent) daily p.o.</td>
<td>Competitive AR inhibition</td>
</tr>
<tr>
<td>Bicalutamide</td>
<td>Non-steroidal antiandrogen</td>
<td>50 mg (combination dose) or 150 mg (single agent) daily p.o.</td>
<td>Competitive AR inhibition</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Corticosteroid</td>
<td>5–10 mg daily p.o.</td>
<td>Adrenal suppression</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Corticosteroid</td>
<td>0.5–2 mg daily p.o.</td>
<td>Adrenal suppression</td>
</tr>
<tr>
<td>Abiraterone acetate</td>
<td>Androgen synthesis inhibitor</td>
<td>1000 mg daily p.o. with prednisolone 5 mg twice daily p.o.</td>
<td>Reduced androgen production within adrenal glands and prostate cancer cells</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>AR inhibitor</td>
<td>160 mg daily p.o.</td>
<td>Competitive AR inhibition, block of AR translocation to the nucleus</td>
</tr>
</tbody>
</table>

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

- **Hypothalamus**
  - GNRH
  - FSH/LH
  - ACTH

- **Pituitary**
  - GONADS
    - TESTES: Cholesterol → Testosterone
    - OVARIIES: Cholesterol → Oestradiol

- **Adrenals**
  - Cholesterol → Androstenedione

- **Peripheral Fat**
  - Peripheral conversion by aromatase to testosterone or oestrone

- **Hormone Responsive End-Organ**
  - e.g. PROSTATE
    - 5α-reductase
    - Testosterone → Dihydrotestosterone
    - Androgen receptor (AR) activation
    - Nuclear translocation and activation of the hormone responsive elements with the genome
  - e.g. BREAST
    - Oestradiol
    - Dihydroxytestosterone

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*Testosterone, dihydrotestosterone, androstenedione, circulating oestrogens and inhibin contribute to negative feedback.

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GnRH, gonadotrophin-releasing hormone; LH, luteinizing hormone.

Figure 1
References


What's new

- The mechanisms behind resistance to hormonal therapies are being better characterized.
- New drugs targeting these mechanisms have shown a survival advantage over previous best care and have entered routine practice.
- Further agents overcoming resistance to these newer agents are now being studied.
- In breast cancer, pathway inhibitors are used in combination with aromatase inhibitors to overcome resistance.
- In prostate cancer these are abiraterone acetate and enzalutamide.