Hormonal therapy for cancer

Jacinta Abraham
John Staffurth

Abstract

Hormone therapy is an extremely effective and relatively non-toxic therapy for both breast and prostate cancer, and some other cancers demonstrate minor levels of hormone sensitivity. Serum levels of oestradiol and testosterone are controlled by the hypothalamic-pituitary-gonadal pathway. In premenopausal women, oestradiol is primarily produced from the ovaries, whereas in postmenopausal women peripheral conversion of adrenal androgens by aromatase within peripheral fat predominates. In premenopausal women with breast cancer and men with prostate cancer, hormonal therapy is primarily achieved by castration. In postmenopausal women, selective oestrogen receptor modulators (e.g. tamoxifen) or aromatase inhibitors are used. Hormone therapy is often part of curative therapy, either neoadjuvantly (to reduce the size of the primary cancer prior to radical surgery or radiotherapy), or adjuvantly (to reduce the risk of recurrence). Hormone therapy is also highly effective in patients with incurable locally advanced or metastatic disease. The majority of patients respond, often with a prolonged period before there is evidence of relapse. Unfortunately, most patients do eventually relapse. However, there are increasing numbers of active agents entering clinical practice or clinical trials in this 'castration-resistant' setting.

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

Jacinta Abraham ***BMedSci BMBS MRCP FRCR*** *is a Consultant Clinical Oncologist at Velindre NHS Trust, Cardiff. UK. She qualified from Nottingham Medical School in 1990. She completed her clinical oncology training in South-East Wales and was appointed to Velindre NHS Trust in 2003. She specializes in breast cancer and has research interests in bisphosphonates, infertility in cancer and secondary breast cancer. Competing interests: none declared.*

John Staffurth ***MBBS MD MRCP FRCR*** *is a Clinical Senior Lecturer in Oncology at Cardiff University, Cardiff, UK. He qualified from Guy's Hospital, London University, UK in 1992. After basic medical training, he pursued a career in clinical oncology, training on the pan-Thames rotation. His research interests include prostate and bladder cancer, radiotherapy and immunology. Competing interests: none declared.*

Aetiology

Hormones have been implicated in the aetiology and development of several cancers. This chapter will concentrate on the management of breast and prostate cancers where the impact of hormone therapy is most clinically significant. Other cancers which may exhibit hormonal dependence include ovarian and endometrial cancers, melanoma and meningioma.

Increased exposure to endogenous or exogenous oestrogens may be linked to the development of breast cancer as shown in Table 1. On the other hand, 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. The evidence in prostate cancer was established by Charles Huggins and colleagues in the early 1940s. They showed that the growth of a high proportion of human prostate cancers was critically dependent on the presence of circulating androgens. The Nobel Prize for medicine was awarded to Charles Huggins in 1966 following the discovery that surgical orchidectomy was a successful treatment for metastatic prostate cancer.

Hormone synthesis

Oestrogen synthesis

Oestrogen is synthesized from cholesterol following a series of reactions which occur mainly in the parafollicular ovaries in premenopausal women and the adrenals in postmenopausal women.

In premenopausal women, oestrogen production is cyclical and controlled under negative feedback via the hypothalamic-pituitary-gonadal axis (Figure 1). The anterior pituitary, under the control of the gonadotrophin-releasing hormone (GnRH, also known as LHRH), synthesizes and secretes luteinizing hormone (LH) and follicle-stimulating hormone (FSH). GnRH is a 10-amino acid polypeptide that is released in pulses from the hypothalamus with a circadian rhythm under direct feedback control of circulating androgens and oestrogens. GnRH reacts with its receptor on the cells of the anterior pituitary, leading to LH and FSH release. These stimulate the ovarian theca externa

Hormonal risks for breast cancer

Risk factors for breast cancer	Protective factors for breast cancer
Early menarche	Breast-feeding
Late menopause	Young age at full-term pregnancy
Nulliparity	
Obesity	
Hormone replacement therapy	

Table 1

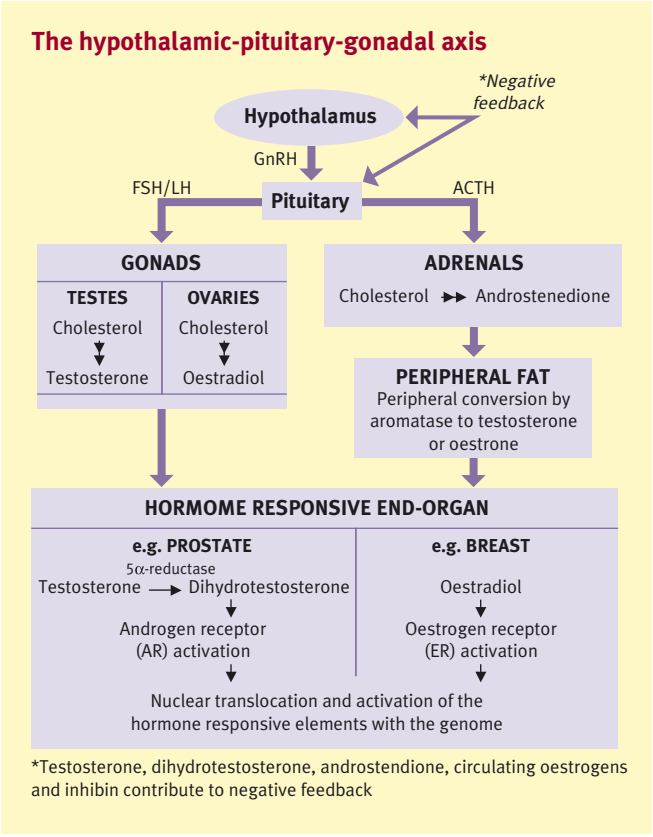

Figure 1

and granulosa cells to produce oestradiol. The feedback loop is completed by the production and secretion by ovarian granulosa cells of the polypeptide inhibin, which inhibits FSH release by pituitary gonadotrophs.

In postmenopausal women, the main site of oestrogen synthesis is adipose tissue. Here, adrenal androgens, in particular androstenedione, are converted in the peripheral tissues by the p450 enzyme, aromatase, to oestrone. Oestrone is then converted to oestradiol by 17β–OH dehydrogenase. Postmenopausal synthesis is not under cyclical control but varies depending on environmental and genetic factors (e.g. obesity).

Androgen synthesis

In men, the main circulating androgen is testosterone, 90% of which is produced by the Leydig cells of the testis. This production is controlled by the hypothalamic-pituitary axis, with hypothalamic GnRH controlling the release of LH and FSH from the anterior pituitary, as above.

Testosterone is secreted by the testes and circulates in serum primarily bound to the glycoprotein, sex hormone-binding globulin. The remaining circulating androgens, such as dihydroxyandrostenedione (DHA), androstenedione and DHA sulphate, are produced in the adrenal cortex from cholesterol.

All circulating androgens, irrespective of source, are metabolized by the enzyme 5α reductase within the prostate to the more biologically active 5α dihydrotestosterone (DHT). DHT binds to the androgen receptor with 3 to 5 times greater affinity than testosterone itself.

Hormone receptors

Oestrogen and progesterone receptors

In breast cancer, approximately 80% of all postmenopausal women and 50% of all premenopausal women will have hormone receptor-positive disease. The degree of positivity is defined by the levels of expression of both the oestrogen (ER) and progesterone receptors (PR), which are routinely measured by immunohistochemical methods in breast tissue biopsies of newly diagnosed cases. In breast cancer, systemic treatment and, to some extent, prognosis will be guided by the hormone receptor status.

Androgen receptors

In contrast, the measurement of the androgen receptor is not routinely performed in prostate cancer as it has no therapeutic or prognostic value. This is because both hormone-dependent and non-dependent prostate cancers possess functioning androgen receptors.

Hormone therapy in breast cancer

Ovarian ablation

It is important to distinguish between hormone therapy in the premenopausal and postmenopausal settings. In the premenopausal woman the most obvious and direct way to reduce oestrogen production is to suppress the ovaries. In practice, this may be achieved by chemical ablation, radiation to the ovaries or surgical oophorectomy. Chemical ablation is reversible and achieved by using a gonadotrophin-releasing hormone agonist (GnRHa or LHRHa) such as goserelin, which can be given as either a monthly or 3-monthly depot injection.

Other hormonal agents in breast cancer

There are an ever increasing number of hormonal treatment options available for the treatment of breast cancer. A list of the different licensed drugs, their type, mode of action and dose is given in Table 2. The most commonly used treatments, such as tamoxifen and aromatase inhibitors (AIs), will be discussed in more detail.

Tamoxifen: this is the most widely used and researched anti-oestrogen in breast cancer. It is described as a selective oestrogen receptor modulator (SERM) because of its complex actions on oestrogen receptors, which are both a predominantly antagonist and partial agonist effect. In ER-positive early breast cancer, five years of tamoxifen after surgery reduces the annual recurrence rate by 41% and annual mortality rate by 34%.[1]

Tamoxifen may be used in both premenopausal and postmenopausal women. The main side effects are hot flushes, night sweats and vaginal discharge. There is an increased risk of thrombotic events and it should be avoided in individuals with a history of deep venous thrombosis or pulmonary embolus. Symptoms of abnormal vaginal bleeding should be promptly evaluated because of the small but statistically significant increase in endometrial cancer, due to its partial agonist actions.[2]

Aromatase inhibitors (AI): third generation aromatase inhibitors have been developed in recent years. The results of several