Endocrine therapy for cancer

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Abstract

Endocrine therapy is widely used to treat cancers whose growth is dependent on hormonal stimulation, most commonly breast, prostate and endometrial cancers. The principles behind its use, indications, different medications available and some of the evidence to support its use are described. Endocrine therapies avoid the toxicities associated with chemotherapy, but do have recognized side effects that can impact on quality of life.

Keywords Androgen; breast cancer; endocrine therapy; endometrial cancer; LHRH; neuroendocrine tumours; oestrogen; prostate cancer

Introduction

In 1896, Thomas Beatson, a graduate of the University of Edinburgh working in Glasgow observed regression of a locally advanced breast cancer following bilateral oophorectomy and the potential use of hormone therapy to treat cancer was first demonstrated, even before the discovery of the hormone itself.

Hormonal therapy is now one of the major modalities of pharmacotherapy in cancer care and is often used as the only treatment or combined with other treatments such as surgery, radiotherapy and chemotherapy. It may also be used in the neoadjuvant setting as a treatment to shrink tumours prior to definitive surgery.

The sex steroid hormones include androgens, oestrogens and progesterone and these are important drivers of proliferation in breast and prostate cancer cells. Endocrine therapy modulates hormone-dependent pathways that results in a decrease in rates of proliferation in cancer cells.

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This can be achieved either by the administration of exogenous agents that bind to hormone receptors or modulating pathways to achieve down regulation or by ablation of the source of endogenous hormone production by surgery, chemicals or radiation.

The cancers most commonly treated with endocrine therapy originate from the breast, prostate and endometrium.

Breast cancer

Breast cancer is the most frequently diagnosed cancer in women and the leading cause of death from cancer in women worldwide. Breast cancer is an extremely heterogeneous disease with a wide range of molecular subtypes but can be broadly categorized into two groups in terms of hormone sensitivity as either positive or negative. Hormone sensitive cancers express receptors to either oestrogen (ER), progesterone (PR) or both. Approximately 75% of invasive breast cancers in postmenopausal women and 50% of the breast cancers in premenopausal women are hormone-receptor positive.

When reference is made to the receptor status of a breast cancer, it is the ER status that is most commonly being referred to. The degree of expression of ER and PR receptors varies and is predictive of responsiveness of the cancer to hormonal therapy. ER and PR can be quantified and there are a variety of methods in clinical use. The Allred score incorporates the percentage of cells that test positive for receptors (from 0 to 5), along with the intensity of receptors (0–3) in a combined score ranging from 0 to 8. Alternatively the percentage of cells is multiplied by intensity to provide a histoscore (0–300) although others just estimate the percentage of cells staining for ER and PR. Tumours that have both ER and PR expression have a >70% chance of responding to hormonal manipulation in contrast to ER/PR-negative tumours, which do not respond.

There are a number of ways of reducing the hormonal stimulation of breast cancers. These include:

1. Suppression/ablation of ovarian function by:
   - Surgical (usually laparoscopic) oophorectomy.
   - Short course of pelvic radiotherapy.
   - Chemical ablation using the administration of luteinizing hormone releasing hormone (LHRH) agonists such as Goserelin which causes a down-regulation of pituitary LHRH receptors, leading to a decrease in luteinizing hormone/follicle-stimulating hormone secretion, which in turn leads to reduced serum oestradiol levels. This agent is given monthly by injection and the effects are reversible

   In current treatment protocols ovarian suppression is reserved for higher risk patients (young age, large tumour size, high grade, multiple nodes positive), metastatic disease and palliation.
2. Administration of selective oestrogen receptor modulators (SERMs) such as:
   - **Tamoxifen**: this works by binding to activating regions of the oestrogen receptor by competitive antagonism. It is first-line adjuvant treatment in premenopausal women but is also used in postmenopausal women intolerant to other therapy and in cancer palliation. It is given orally at a standard dose of 20 mg once a day. The standard length of treatment has been for a long time 5 years, but recent

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research suggests that longer durations of endocrine therapy reduce recurrence rate so patients now take 5 years tamoxifen followed by 5 years of an aromatase inhibitor (if they are postmenopausal after 5 years of tamoxifen) or 10 years of tamoxifen. Tamoxifen is generally well tolerated, however, patients should be counselled regarding side effect profile that include hot flushes, vaginal discharge/dryness, nausea and weight gain. There is a small but significant risk of thromboembolism but this is mainly in postmenopausal women so it should not be used in anyone with a history of blood clots or a coagulation disorder. There is a small risk (2 in 1000 annually) of endometrial cancer again in postmenopausal women and patients should be aware of the importance of consulting their GP if new gynaecological symptoms develop.

- **Raloxifene**: this has been used in prevention studies and is used for osteoporosis; both tamoxifen and raloxifene increase bone density in postmenopausal women. Raloxifene has significantly less endometrial stimulation but unfortunately is less effective than tamoxifen in its effects on breast cancer.

3. Administration of aromatase inhibitors (AIs) that reduce oestrogen production in postmenopausal women. In postmenopausal women the majority of circulating oestrogen is produced in peripheral tissues by conversion of androgens produced by the adrenal gland via the aromatase enzyme as opposed to the ovaries in premenopausal women. The mechanism of action is the inhibition the enzyme aromatase which reduces circulating and intratumoural oestrogen levels. The three commonly used drugs are: anastrozole, letrozole (non-steroidal aromatase inhibitors) and exemestane (steroidal aromatase inhibitor).

   Side effects of aromatase inhibitor's include arthralgia, osteoporosis and hypercholesterolaemia. Patients commenced on aromatase inhibitors should have a baseline DEXA scan (dual energy X-ray absorptiometry) to assess their bone density. If this detects a reduction in bone mineral density (BMD) then, depending on the level of loss, then dietary advice (a calcium rich diet), light exercise, smoking cessation, calcium and vitamin D supplementation and/or bisphosphonate therapy (zoledronic acid) may be appropriate.
4. Miscellaneous: A new generation of pure antioestrogens is in trials. Fulvestrant is an established pure antioestrogen also known as a selective oestrogen receptor downregulator (SERD). It is injectable and is not widely used. Oestrogen in high doses is also effective – something known as oestrogen paradox. Progestins at high doses such as megestrol acetate are also effective in breast cancer but also used in endometrial and prostate cancer.

Hormonal therapy in breast cancer can be used in the context of primary hormonal therapy, neoadjuvant therapy, adjuvant therapy, palliative therapy and more recently for chemoprevention.

Neoadjuvant hormonal therapy

Neoadjuvant endocrine therapy can be used to downstage or shrink ER-positive tumours to either make an inoperable tumour become operable or to allow less invasive breast conservation surgery (BCS) usually in the form of wide local excision rather than mastectomy.

The IMPACT trial[1] demonstrated that more than 40% of postmenopausal breast cancer patients initially requiring mastectomy at diagnosis were suitable for breast conservation surgery (BCS) following neoadjuvant treatment with anastrazole.

Primary hormonal therapy

Primary hormonal therapy can be used to treat postmenopausal women who have ER-positive cancers but who are either unfit for surgery or who decline surgical treatment. No difference in overall survival was reported in a 2014 Cochrane review[2] that compared primary hormonal therapy with surgery, although there was a higher rate of disease relapse reported with primary hormonal therapy. There is currently concern that some women >75 years are being treated inappropriately by primary endocrine therapy based on their age alone, rather than with surgery and adjuvant treatment. Few women are unfit for surgery so most women get neoadjuvant endocrine therapy followed by surgery with or without radiotherapy.

Perioperative endocrine therapy

There is ongoing research investigating whether commencing endocrine therapy in the weeks prior to surgical excision improves outcomes. The POETIC trial seeks to determine whether 4 weeks of preoperative endocrine therapy with an aromatase inhibitor followed by standard adjuvant therapy improves outcome compared with standard adjuvant therapy alone in postmenopausal women with hormone receptor-positive cancer. It will also investigate whether measurement of Ki67, a marker of tumour proliferation, in the excised cancer can predict future response to adjuvant endocrine therapy. Data from Edinburgh Breast Cancer Research Group does show that early changes in proliferation predict for long term benefit from adjuvant hormone therapy.

The IMPACT trial determined the clinical significance of the level of tumour cell proliferation during endocrine therapy for breast cancer, by measuring the expression of Ki67 in tumour biopsy samples taken before and after 2 weeks of presurgical treatment with anastrozole or tamoxifen or the combination of anastrozole plus tamoxifen. Analysis showed that higher Ki67 expression after 2 weeks of endocrine therapy was statistically significantly associated with lower recurrence-free survival.

Adjuvant therapy

All patients with ER-positive cancers should be offered endocrine therapy postoperatively, unless contraindicated. Tamoxifen is the drug of choice for premenopausal women. A review of tamoxifen trials confirmed that 5 years of tamoxifen reduces the risk of death by 31% per annum in receptor-positive breast cancer patients.[3]

The 5-year period of treatment is under review following the results of several trials (ATTom[4] and ATLAS[5]) that have shown that women who took adjuvant tamoxifen for 10 years had lower recurrence rates and a decrease in breast cancer mortality after 10 years had passed.

Aromatase inhibitors are prescribed for postmenopausal women. The results of trials, which randomized women to receive letrozole or tamoxifen (BIG-1-98[6]) or tamoxifen versus

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