Endocrine therapy in cancer care

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Abstract
Endocrine therapy is an important way to manage cancers whose growth is dependent on hormonal stimulation, namely breast, prostate and endometrial cancers. This article describes the principles behind their use, the indications for use, the different medications available and some of the evidence to support their use. Endocrine therapies avoid the toxicities associated with chemotherapy, but often have side effects that impact on quality of life too.

Keywords Androgen deprivation therapy; anti-oestrogens; breast cancer; endocrine therapy; LHRH agonist; prostate cancer

Introduction

Hormonal therapy is one of the major modalities of pharmacotherapy in cancer care and is often used as primary treatment or alongside other treatments such as cytotoxic chemotherapy, other biological agents, surgery and radiotherapy. Endocrine therapy was discovered following Beatson's observation of the regression of locally advanced breast cancer following bilateral oophorectomy over 100 years ago.

Steroid hormones are important drivers of gene expression in cancer cells such as breast cancer, and are also essential for the growth of tumour cells such as prostate cancer. Endocrine therapy manipulates hormone-dependent pathways that lead to increased gene expression and carcinogenesis. This can be achieved either by the administration of exogenous agents that interact with hormone receptors to achieve down regulation or the ablation of the source of endogenous hormone production by surgery, chemicals or radiation.

After a variable period of time some cancers treated with hormonal therapy develop resistance to therapy and pose challenges in the treatment of cancers. However, this is often offset by switching to alternative hormonal agents.

Cancers commonly treated with endocrine therapy include breast, prostate and endometrial tumours.

Breast cancer

Approximately 75% of invasive breast cancers in postmenopausal women and 50% of the breast cancers in premenopausal women will be hormone receptor positive. There are two types of hormone receptors in breast cancer, oestrogen and progesterone receptors and each has two sub-types, but reference is most commonly made to oestrogen receptors. The degree of expression of these receptors varies and is predictive of the responsiveness of the cancer to hormonal therapy. Tumours with both ER and PR expression have a >70% chance of responding to hormonal manipulation in contrast to ER/PR negative tumours, which hardly respond. In an unselected patient population 30% of tumours will respond to hormonal therapy, but it is generally advised that systemic hormone therapy is not commenced until the hormone receptor status is known.

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

Suppression of ovarian function by:

- Surgical oophorectomy which is now usually performed laparoscopically.
- Radiotherapeutic oophorectomy using a short course of radiotherapy to the pelvis (total dose of 10–20 Gy delivered in 5–10 daily fractions).
- 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 subcutaneous injections into the anterior abdominal wall and the effects are reversible.

Today ovarian suppression is usually used for metastatic disease and palliation rather than for first-line treatment.

Administration of selective oestrogen receptor modulators (SERMs) such as:

- **Tamoxifen**, which works by binding onto the activating regions of the oestrogen receptor and blocks the action of oestrogen. It is usually used as adjuvant treatment in premenopausal women. It is given orally at a standard dose of 20mg once a day. It has recently become apparent that although a tumour may be ER positive, some patients do not respond in the same way and this may be due to the way that people metabolize tamoxifen. This is due to a genetically determined deficiency of the cytochrome P-450 enzyme that activates tamoxifen to an active metabolite, endo-tamoxifen.

  Side effects include hot flushes, vaginal discharge, nausea and weight gain. It is, however, linked with a small but significant risk of thromboembolism and stroke so should not be used in anyone who has a thrombotic tendency. There is a small risk of endometrial cancer in postmenopausal women.

- **Aromatase inhibitors (AIs)**: These oral drugs are used in postmenopausal women only. They reduce serum oestradiol by inhibiting the p450 enzyme aromatase which converts androgens into oestradiol in peripheral tissues.

  The three most common drugs are: anastrozole, letrozole (non-steroidal aromatase inhibitors) and exemestane (steroidal aromatase inhibitor).

  Side effects include arthralgia, osteoporosis and hypercholesterolaemia. NICE[1] guidelines recommend that all women starting on aromatase inhibitors should have a

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baseline DEXA scan (dual energy X-ray absorptiometry) to assess their bone density. If this detects osteopenia or osteoporosis then appropriate treatment should be given together with the aromatase inhibitor.

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

Neoadjuvant hormonal therapy and primary hormonal therapy

The main benefit of hormonal therapy as neoadjuvant therapy is to attempt to downstage tumours that are ER positive in order to avoid mastectomy or to make an inoperable tumour operable. Studies have shown that aromatase inhibitors are more effective than tamoxifen in the context of neoadjuvant therapy for postmenopausal women. More than 40% of patients initially requiring mastectomy were suitable for breast conservation surgery (BCS) in a neoadjuvant trial in favour of aromatase inhibitors,[2] but the optimum duration of neoadjuvant therapy is unclear.

Primary hormonal therapy is commonly used to treat postmenopausal women who have ER positive cancers but who are either unfit or decline surgical treatment. No difference in overall survival was reported in a recent Cochrane review[3] which compared primary hormonal therapy with surgery, albeit a higher rate of disease relapse was reported with primary hormonal therapy. There is currently some concern that some women >75 years are being treated inappropriately by endocrine therapy alone, rather than surgery and adjuvant treatment.

A current subject of research is the identification of short-term molecular markers that may be able to predict long-term outcomes for treatments and patients. Tumour expression of the proliferation antigen Ki67 is widely used to assess the prognosis of cancer patients. A change in the expression of Ki67 after short-term exposure of patients to therapeutic agents is frequently used as a pharmacodynamic marker of efficacy, particularly among breast cancer patients before undergoing surgery. The IMPACT trial[2] 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, whereas higher Ki67 expression at baseline was not. Larger baseline tumor size and lower oestrogen receptor level after 2 weeks of treatment were also statistically significantly associated with poorer recurrence-free survival. The data indicates that measurements of tumour Ki67 level after short-term endocrine treatment may improve the prediction of recurrence-free survival by integrating the prognostic value of Ki67 level at baseline with changes in Ki67 level that are associated with treatment benefit. The aim of the recently closed POETIC trial was to ascertain whether 4 weeks of aromatase inhibitors at the time of surgery reduces the recurrence rate, and whether testing cancer cells after 2 weeks of hormone therapy can predict response to treatment.

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.[4] A review of several longer trials[5] (ATTom and ATLAS trials) has shown that women who took adjuvant tamoxifen for 10 years had lower recurrence rates and a decrease in breast cancer mortality. Combining the results of these studies produced significant results in favour of ten years of adjuvant therapy.

Aromatase inhibitors are prescribed for postmenopausal women. The results of trials, which randomized women to receive letrozole or tamoxifen (BIG-1-98) and which randomized women to tamoxifen versus anastrozole (ATAC) also reported fewer recurrences for patients taking aromatase inhibitors. These results led NICE[1] to advise that 5 years of an aromatase inhibitor should be standard care for all ER-positive postmenopausal patients. Women who are taking tamoxifen should also be reviewed and changed to an aromatase inhibitor after 5 years if they are postmenopausal. After 5 years of treatment all patients should be reviewed and those at high risk of recurrence as determined by Adjuvantonline[6] or PREDICT[7] are advised to continue with a further five years of treatment.

Palliative therapy in metastatic disease

When metastatic or local recurrence occurs, endocrine therapy should be considered as first-line treatment for the majority of patients with hormone receptor positive disease, particularly where disease is confined to the bones. Chemotherapy tends to be preferred when significant visceral disease is present.

Tamoxifen is first-line treatment for premenopausal, oestrogen receptor positive patients with metastatic disease. Where metastatic disease occurs whilst on tamoxifen, ovarian suppression in the form of oophorectomy, pelvic radiation or LHRH agonists is considered.

Aromatase inhibitors are the drug of choice in postmenopausal patients and a switch from a steroidal to a non-steroidal agent is considered when there is no objective benefit with one form of AIs. Fulvestrant is another anti-oestrogen and an alternative in the management of advanced tamoxifen resistant disease in postmenopausal women. Unlike tamoxifen, fulvestrant does not have agonist properties.

Occasionally progestogens, such as medroxprogesterone acetate and megestrol acetate are used in both pre and postmenopausal women when anti-oestrogens have failed. Side effects may include nausea, fluid retention and weight gain.

Chemoprevention

Chemoprevention is the prevention of clinically relevant cancers by pharmacological agents that inhibit or reverse the process of carcinogenesis. It has recently been recommended as a possible method of managing women at increased risk of developing breast cancer, including patients with BRCA1 and BRCA2 mutations. Unfortunately BRCA1 carriers tend to develop ER negative tumours and BRCA2 carriers tend to develop ER positive cancers.

SERMS such as tamoxifen and AIs have been used in chemoprevention. There have been inconsistent results from trials

