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BREAST CANCER AND ADJUVANT ENDOCRINE THERAPY

- **Breast cancer is common and associated with high survival rates; many patients treated with curative intent will go on to receive adjuvant endocrine therapy for at least 5 years**
- **Adverse effects associated with endocrine therapy (e.g. aromatase inhibitors and tamoxifen) potentially affect the patient's quality of life and adherence to treatment; strategies to tackle these adverse effects may improve patient outcomes**
- **Considerations for the overall health of patients include optimising bone health, protecting cardiometabolic health, counselling on family planning and promoting the reduction of harmful lifestyle factors**
- **Prescribing practices for this group of patients include developing an awareness of common drug interactions, lifelong avoidance of the use of systemic oestrogen or progesterone hormonal therapies (under specialist advice only) and caution around medications which can cause dependency and addiction issues, and medications associated with renal impairment**

CANCER SURVIVORSHIP IN GENERAL

General Practitioners (GPs) support patients with cancer in many ways over their individual and unique journeys from the risk reduction phase to the screening and diagnosis stage to communicating with secondary care, managing medications, adverse effects of treatment and symptom control. This role is recognised and valued by patients and GPs alike.[1, 2] It is estimated that at least 1 in 3 people will develop cancer in their lifetime.[3] Breast and prostate cancer are the commonest newly diagnosed invasive cancers in Ireland in women and men (most common incident cancers in 2018-2020 at 32% and 30% respectively, excluding non-melanoma skin cancer [NMSC]); the prognosis is good for both diseases, with the overall 5 year survival above 80%.[4]

Many patients with breast cancer undergoing treatment with "curative intent" will go on to receive oral endocrine based anti-cancer medications (i.e. adjuvant endocrine therapy) for prolonged periods of time as they move into the remission phase of their survivorship journey.[5] These patients whose prognosis is good may receive lower intensity follow up and reduced surveillance from their oncology specialist.[6] There is a growing recognition of the nuanced care needs of patients in order to live well with and beyond cancer in the longer term. The National Cancer Survivorship Needs Assessment recognises a gap to be filled in order for healthcare providers to be able to effectively and confidently manage the increased risk of medical problems, psychosocial distress and the increased risk of further cancer diagnoses or recurrence of disease.[7]

This bulletin will discuss the adjuvant endocrine therapies which patients with **breast cancer** are commonly prescribed. Systemic hospital based anti-cancer therapies for the active treatment phase of breast cancer are not the focus for this bulletin. There is a separate bulletin covering adjuvant endocrine therapies used in patients with prostate cancer.

AN INTRODUCTION TO BREAST CANCER

There were 3507 new cases of invasive breast cancer diagnosed annually in Ireland between 2017 to 2019 equating to a cumulative lifetime risk of diagnosis of 1 in 10, with breast cancer making up 31% of all invasive cancers in females.[8] The majority (>70%) of patients are stage 1 or 2 at diagnosis, 59% of all patients diagnosed with breast cancer receive adjuvant endocrine therapy also known as hormone therapy within the first year; overall the 5 year net survival of patients diagnosed with breast cancer is 88%.[8]

Information on the risk factors for breast cancer can be found here. Further reading around how breast cancer presents can be obtained here. The description of the stages of breast cancer can be obtained here.

Breast cancer has traditionally been staged by tumour size, nodal involvement and metastatic involvement but the integration of molecular markers with disease extent has led to a better estimation of individual patient

prognosis.[9] Characterisation of breast cancer by immunohistochemical markers (e.g. oestrogen receptor [ER], progesterone receptor [PR] and HER2 status), proliferation protein marker, genomic markers and immunomarkers is the basis for the targeted treatment approach.

ER positive (+) tumours are treated with chemotherapy and/or radiotherapy and 5 to 10 years of endocrine therapy based on the individual patient risk assessment.[10]

ENDOCRINE THERAPIES USED IN THE TREATMENT OF BREAST CANCER

Oestrogen is the main hormone involved in the growth of breast tumours, therefore oestrogen deprivation is a necessary and logical therapeutic approach albeit with many potential adverse effects.[11]

Endocrine therapy includes tamoxifen (a selective oestrogen receptor modulator) and aromatase inhibitors (AIs) (non-steroidal and steroidal).

International guidelines provide recommendations on the use of endocrine therapies for the treatment of breast cancer.[12-15] In general tamoxifen is used to treat pre-menopausal women and men with ER+ breast cancer and aromatase inhibitors (AI) are used for treatment of postmenopausal women whom have ER+ disease; some postmenopausal women may receive tamoxifen followed by AI or tamoxifen alone.

For ER+ disease only, allocation to about 5 years of adjuvant tamoxifen reduces the annual breast cancer death rate by 31%.[16] Extended treatment beyond 5 years, in some patients, can reduce the risk of recurrence and mortality.[17]

Table 1 summarises the precautions, potential drug interactions and common adverse effects associated with the endocrine therapy currently available in Ireland.[18-21]

Table 1: Precautions, adverse effects and interactions of aromatase inhibitors and tamoxifen[18-23]

Drug classification Drug	Precautions include:*	Very common (≥1/10)/common (≥1/100 to <1/10) adverse effects include:*	Potential drug interactions include:*
Selective oestrogen receptor modulator			
Tamoxifen	↑ risk of VTE, endometrial cancer and uterine sarcoma; association with menstrual abnormalities, SCAR and angioedema; C/I in pregnancy (delay pregnancy 9 months after ceasing treatment); not recommended in breastfeeding; CYP2D6 poor metabolisers have ↓ levels of endoxifen (important metabolite of tamoxifen) **Monitor** FBC, LFTs, Ca and for visual changes	Anaemia; fluid retention; dizziness; ↑ TGs, CVA, sensory disturbances; cataracts; retinopathy; hot flushes; GI effects; changes in LFTs; fatty liver; skin rash; alopecia; myalgia; menstrual abnormalities; hypersensitivity; uterine fibroids; fatigue; thromboembolic events	Warfarin; avoid potent CYP2D6 inhibitors (e.g. paroxetine, fluoxetine)
Aromatase inhibitors**			
Anastrozole (Non-steroidal aromatase inhibitor)	Caution in patients with hepatic and renal impairment; may cause ↓BMD-assess at baseline and monitor and treat osteoporosis as appropriate during therapy; C/I in pregnancy and breastfeeding; risk of tendonitis/tendon rupture with letrozole Avoid co-administration of oestrogen containing medicines as this may negate the pharmacological action **Monitor** FBC, LFTs and Ca	Anorexia; ↑cholesterol; depression; headache; fatigue; hot flushes; GI effects; ↑LFTs, alopecia; allergic reactions; arthralgia/myalgia; osteoporosis; bone pain; vaginal bleeding; hypertension and palpitations (letrozole)	Avoid co-administration with tamoxifen or oestrogen containing medicines which may ↓ the pharmacological action
Letrozole (Non-steroidal aromatase inhibitor)			
Exemestane (Steroidal aromatase inhibitor)		Anorexia; leucopenia; thrombocytopenia; depression; insomnia; headache; dizziness; carpal tunnel syndrome; hot flushes; GI effects; ↑LFTs, alopecia; skin adverse effects; allergic reactions; arthralgia/myalgia; osteoporosis; bone pain; vaginal bleeding	May be affected by potent CYP 3A4 inducers resulting in ↓ efficacy

BMD-bone mineral density; Ca-calcium; C/I-contraindicated; CVA-cerebrovascular accident; FBC-full blood count; GI-gastrointestinal; LFTs-liver function tests; SCAR-serious cutaneous adverse reactions; TGs-triglycerides; VTE-venous thromboembolism;

*full prescribing details are in the Summary of Product Characteristics**only postmenopausal women should receive aromatase inhibitors (menopausal status may need to be confirmed)

Tamoxifen is a competitive antagonist of oestrogen at the receptor site and it also has some agonist activity. This protects bone health but increases the risk of venous thromboembolism (VTE) and vaginal bleeding (due to aberrant endometrial proliferation).[24] Tamoxifen is a prodrug and most of its therapeutic effects are as a result of the metabolite endoxifen. Cytochrome (CYP) P450 isoenzyme 2D6 is the most

important enzyme in the production of endoxifen and any drugs that inhibit CYP2D6 may reduce tamoxifen efficacy, with this effect varying from person to person.[25] This is relevant for medications such as some selective serotonin reuptake inhibitors (SSRIs), herbal and OTC products, anticoagulants, rifampicin, terbinafine, HIV medications, cardiac medications and more. Further details are provided in the Summary of Product Characteristics (SmPC) here.[22, 26-30].

Aromatase inhibitors (AIs) suppress oestrogen levels by inhibiting/inactivating the aromatase enzyme which is responsible for the synthesis of oestrogen from androgenic substrates (such as the synthesis of oestrone from androstenedione and oestradiol from testosterone) and unlike tamoxifen have no partial agonist effect.[31] Non-steroidal AIs include anastrozole and letrozole, and exemestane is a steroidal AI.

ADVERSE EFFECTS

The adverse effects associated with AIs and tamoxifen are problematic and can affect quality of life. Evidence shows that this influences adherence to treatment.[32-34] As seen in table 1, the symptoms experienced by patients taking AIs and tamoxifen include hot flushes and genitourinary symptoms, sexual dysfunction (e.g. loss of libido), cognitive problems (e.g. concentration and memory problems), hair thinning, sleep difficulties and fatigue, weight gain, mood issues, headaches, myalgias and joint pain.[35-37] Specific to tamoxifen is the increased risk of VTE, endometrial cancers, polyps and fibroids, fatty liver disease and eye problems.[17] Tamoxifen has also been associated with ophthalmological complaints such as dry eye and irritation and issues such as cataracts, retinopathy and maculopathy.[38] While some evidence suggests that there is an increased risk of stroke associated with tamoxifen, the absolute risk is small and some evidence suggests a protective effect.[39-42] AIs also increase cardiometabolic risk by increasing adiposity, risk of diabetes and hyperlipidaemia and they are associated with an increased risk of osteoporosis and bone and joint pain, carpal tunnel and stiffness.[33, 43]

Users of tamoxifen and AIs have been shown to use numerous adjunctive medications for adverse effect symptom control, which has an additional financial burden for patients.[44] Overall, in comparison to patients with breast cancer not taking oral endocrine therapy, those who take therapy have higher emotional distress, lower quality of life and subjective wellbeing.[45]

ADHERENCE

It is estimated that approximately half of women prescribed endocrine therapy take their treatment less than 80% of the time.[46] The rates of adherence decrease steadily from year 1 to year 5 of endocrine therapy (rates of 37-48%);[47] on average one-third of patients are not adherent to treatment by year 5.[48] In the case of AI therapy, arthralgia was present in 14% of patients at 3 months and compliance decreased over time; overall the level of arthralgia was directly associated with non-compliance.[34]

Many contributing factors have been described around adherence including medication, patient and physician related factors. Evidence suggests that an increased number of symptoms (e.g. fatigue and forgetfulness) at baseline prior to AI therapy is more likely to result in AI discontinuation.[49] Additional factors which contribute to non-adherence include age related factors (very young or very old less likely to be adherent), socioeconomic factors, psychological factors (such as depression), sleep quality and tiredness, severity of disease and more complex medication regimes.[49, 50] Adherence can be a particular issue in pre-menopausal women who are more likely to report adverse effects, compared to women who were menopausal at diagnosis.[51] Those who are more likely to be non-adherent are from minority groups, have more negative medication beliefs and less confidence in their ability to remain on endocrine therapy.[47, 52]

Some approaches which may help to boost adherence include good patient and physician communication, management of adverse effects and social support.[35, 53] Women with a history of breast cancer reported that their physician did not ask them about the genitourinary and sexual symptoms they may be experiencing, which was considered an unmet need in their care.[54] A medication switch could be considered by the oncology team if intolerable adverse effects are flagged; in one study one third of patients who were rotated onto a different AI tolerated the new AI after not tolerating the first choice.[55] In the ATOLL study (non-randomised study of patients that had discontinued anastrozole due to musculoskeletal symptoms) switching from anastrozole to letrozole led to 72% of patients who had previously discontinued AI treatment continuing treatment after 6 months.[56] A specialist approved treatment break is another strategy which is highlighted as an alternative approach to improving adherence.[57] An awareness of this issue is important as healthcare professionals caring for women with breast cancer can build trust and support by explaining the reasons for these therapies, their importance, expected and common adverse effects with ways to tackle these adverse effects should they occur.[57] There is some data which suggests experiencing adverse effects from endocrine therapy may be linked to survival benefit; clinicians communicating this to patients may give them encouragement.[58]

The issues with adverse effects and adherence are important because outcomes are significantly improved by oral endocrine therapy and there is a higher rate of recurrence of breast cancer in women who are non-adherent to treatment.[43,44,59, 60]

MANAGEMENT OF ADVERSE EFFECTS ASSOCIATED WITH ENDOCRINE THERAPY

Pharmacological management of adverse effects is an important aspect of caring for women who are being treated with endocrine therapy.

Vasomotor symptoms are a recognised difficulty for patients who are taking adjuvant oral endocrine therapy; menopausal symptoms can be more severe in those patients on endocrine therapy than those experiencing a natural menopause.[61,62] The use of hormone replacement therapy (HRT) in patients who have a previous diagnosis of breast cancer is not currently advised as part of routine care due to the risk of recurrence; it may be considered as an option under oncological and menopausal specialist advice in rare scenarios.[63-65] *Non-hormonal* options include the use of SSRIs and selective noradrenaline reuptake inhibitors (SNRIs) such as venlafaxine.[66] Gabapentin, a medication usually used for neuropathic pain can be started at a low dose and increased if initially ineffective (taken as a single dose at night-time to avoid day time somnolence).[67, 68] Caution is advised as respiratory depression and dependence can occur with gabapentin.[69] Other options include citalopram or oxybutynin.[67, 70, 71] These non-hormonal medications are found to be less effective than HRT but moderately alleviate the symptoms.[72] **The use of fluoxetine and paroxetine is not advised if taking tamoxifen due to a drug interaction which reduces the bioavailability of its active metabolite**.[73] Adverse effects from SSRIs include gastrointestinal disturbances such as nausea and constipation, headaches, insomnia and interference with sexual function.[74] The anticholinergic side effects of oxybutynin should be considered before initiating treatment particularly for elderly patients (dry mouth, blurred vision, dry eyes, constipation, urinary retention).[75] Medications such as clonidine and pregabalin have been shown to be effective in trials but the adverse effect profile of clonidine (dizziness, sedation, dry mouth) and potential for abuse of pregabalin result in these not being recommended as mainstream options.[76] Neurokinin 3 receptor antagonists (fezolinetant) have been shown to be effective as a non-hormonal option for vasomotor symptoms.[77] This medication is currently not available in Ireland.[78]

Genitourinary symptoms relate to the hypoestrogenic effects on the genital epithelium, and include genital dryness, burning, irritation, and potential downstream effects including dyspareunia, urinary symptoms (e.g. urgency and dysuria) and recurrent urinary tract infections (UTIs).[79] Vaginal dryness is common in women with a history of breast cancer, particularly those taking AIs.[80] *Non-hormonal* options to ameliorate these symptoms include vaginal lubricants, vaginal moisturisers and topical lidocaine. Vaginal lubricants (water based, silicone, plant oil e.g. coconut oil, hyaluronic acid based) should be considered first line options as they are cheap, easily accessible, have been shown to be effective and have a low adverse effect profile, albeit local irritation is reported in some patients.[81-84] The benefits are shown to be superior from silicone pH balanced gels.[85] Application of lidocaine to the vulval vestibule three minutes before penile penetration is a practical solution for dyspareunia.[86]. Patients should avoid irritants such as fragranced washes and wipes and should continue moisturising for maintenance.[87]

Women with a history of breast cancer with refractory or very distressing vaginal atrophy symptoms should be counselled on the use of **localised topical oestrogen, which may be considered where other therapies have not been successful and with the involvement of the specialists** (due to the suspected low but unknown risks of potential systemic absorption).[76, 81, 88, 89] Vaginal oestrogen is available as a cream, tablet or pessary.[90]

Musculoskeletal adverse effects may be relieved by the standard management of joint pains and aches with paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and other analgesic modalities routinely utilised in primary care.[91] Duloxetine can also be useful for AI related joint pains but should be avoided in tamoxifen-users due to the significant drug-drug interaction.[92] There is not enough evidence to recommend the use of vitamin D supplementation, glucosamine and chondroitin therapy for this indication.[93, 94]

Hair thinning is common with 25% of patients taking oral endocrine therapy complaining of this ADR; it usually responds well to topical minoxidil.[95, 96]

Eye problems are an adverse effect associated with endocrine therapy, which may present as dry eye; it occurs as a result of hormone deprivation and meibomian gland dysfunction.[97] This can be managed with topical lubricating eye drops and warm compress therapies.[98] Tamoxifen may be associated with more severe ophthalmological conditions such as retinopathy and potentially cataracts; any patient complaining of concerning visual symptoms should be referred for slit lamp examination.[99, 100]

OTHER ASPECTS TO CONSIDER

Considerations for optimal survivorship care of patients include managing cardiometabolic and bone health, fertility planning, providing contraception for these patients if needed, careful prescribing in general (see further details to follow) and the promotion of social and holistic wellbeing.

Cardiometabolic health: Oestrogen has direct and indirect effects on cardiovascular health by its impact on

coronary vessel wall dilation, thrombosis, lipid function, effect on myocardium and in altering response to ischaemic change.[101] Cancer survivors in general and those who have taken AIs are at an increased risk of diabetes, dyslipidaemia and hypertension.[102, 103] The European Society of Cardiology guideline on cardio-oncology (access here) includes guidance on the optimisation of heart health through risk assessment and monitoring of patients whom have had/are having oral endocrine therapy.[104]

Osteoporosis: Oestrogen deficiency in women with breast cancer is a major cause of accelerated bone loss, with oestrogen deprivation increasing bone turnover, decreasing bone mineral density and it can increase the risk of fracture by 40-50%.[105] Breast cancer survivors who received a DEXA scan at baseline /initiation of AI therapy had a 32% reduced risk of any bone fracture compared with those who did not (review of 22 713 patients stage 0-III breast cancer survivors who received AI treatment).[106] Guidelines are available including a GP based guideline on the management of osteoporosis providing advice around DEXA scans, risk factors, lifestyle and treatment for osteoporosis for patients who are taking oral endocrine therapy.[107, 108] Table 2 summarises some of the key points for the primary care optimisation of bone health in those on AIs.

Table 2: Guidance for the GP to manage bone health optimally for a patient who is taking AI therapy[107]

Baseline assessment of fracture risk
Women undergoing AI therapy who fall within one of the following categories should commence anti-resorptive therapy unless contraindicated: 1. 70 years and over with a BMD T score <-2.5 2. 50 years or older with a minimal trauma fracture (including radiological vertebral fracture) or a high estimated 10 year risk of fracture
General measures to prevent bone loss should be implemented in all women commencing AI
Repeat DEXA should occur in 1-2 years depending on baseline/overall risk

Fertility planning and contraception: Many people with breast cancer remain sexually active and fertile over the course of their treatment but pregnancy during treatment is to be avoided.[109] Suitable contraceptive choices available include copper intrauterine device (reversible) or male or female sterilisation (permanent); condoms and withdrawal practices are not deemed reliable methods and any hormonal contraceptive, including the levonorgestrel intrauterine system (e.g. Mirena®) is to be avoided.[109] Endocrine therapy is not directly toxic to ovaries but the timeline of oral endocrine therapy and the duration may interrupt family planning due to the additional age related decline in fertility.[110] Pregnancy after breast cancer is not contraindicated, some women may be able to pause their oral endocrine therapy after 18-30 months to conceive and the slight delay of treatment initiation after diagnosis of an early breast cancer in order to allow for assisted reproductive techniques does not affect overall survival rates.[111-113]

Non pharmacological interventions are relevant for the holistic care of a patient.

Lifestyle interventions such as weight loss, exercise including weight bearing muscle strengthening exercises,[114, 115] cognitive behavioural therapy (both for the management of mood disorders but also solely for the management of problematic hot flushes, night sweats and fatigue),[92, 116, 117] sleep hygiene, dietary advice including sufficient calcium, vitamin D and protein, reduction of alcohol intake, relaxation therapies, yoga and acupuncture may be beneficial to the patient.[118-123] Exposure to nature, peer supports, relationship supports, assistance with the financial and economic reintegration into society, psychosexual health supports such as a pelvic floor physiotherapy review for manual and biofeedback and vaginal dilator use, and body image counselling may also be considered.[6, 87, 123-128]

Optimising prescribing is important in this cohort of patients with breast cancer; the presence of polypharmacy is associated with greater comorbidity, reduced ability to perform activities of daily living (ADLs) and reduced physical function, therefore acting as a potential marker for frailty.[129] The prevalence of polypharmacy is high, one study showing the level at 50% in younger people and 75% in older people with one of the four commonly prescribed medications being NSAIDs.[130] GPs should consider renal health in patients with breast cancer when prescribing potentially renotoxic medications as poor renal health is associated with worse cancer-specific outcomes.[131] It is important to manage pain appropriately to ensure comfort and maintain function but caution should be exercised around the use of opioid medications long-term unless directed by a specialist as there are long-term adverse effects such as endocrinopathy, neurotoxicity, misuse and abuse.[132] A multimodal holistic approach is advised. Medications such as benzodiazepines and night sedatives are commonly initiated during breast cancer treatment for symptoms such as anxiety and insomnia.[133] Patients with cancer are vulnerable to developing dependency and it has been shown that persistent use is common after curative treatment.[134, 135] This should be managed in a patient centred holistic manner.

Table 3 provides an overview of the key considerations for the overall health of a patient on their breast cancer survivorship journey

Table 3: Guideline for the GP review of the patient on their breast cancer survivorship journey

Ask about medication adverse effects and consider adherence:	Ask about vasomotor symptoms, genitourinary symptoms, sexual dysfunction, joint pain, weight gain, mood issues, PV bleeding.
Consider the presence of any drug interactions:	For example, tamoxifen interacts with some SSRIs such as paroxetine and fluoxetine, anticoagulants, rifampicin and terbinafine
Review cardiometabolic health:	Check weight, waist circumference, blood pressure, lipids, HbA1c, presence of risk factors e.g. smoking and review exercise and diet. Consider baseline ECG
Review bone health:	Perform FRAX score, DEXA, assess need for calcium and vitamin D supplementation, assess falls risk, review risk factors for osteoporosis and recommend exercise
Discuss contraceptive and fertility needs:	Discuss the need for contraception or referral for assisted reproductive techniques
When repeat prescribing try to remember:	Avoid prescribing systemic oestrogen or progesterone products (under specialist advice only), avoid hypnotics and sedatives where possible, caution is advised with renotoxic and analgesic medications
Offer non pharmacological treatments where possible:	Sleep hygiene, exercise, dietary advice, CBT (for management of VMS or a mood disorder), pelvic floor physiotherapy, relaxation therapies

Tips and tricks for repeat prescribing

- Consider potential drug interactions. Ensure all active medications are listed on the repeat prescribing list in the patient's file so that any relevant interactions will be flagged
- Avoid polypharmacy and perform medication review where possible.
- Exercise caution with overuse of NSAIDs or addictive analgesics, sedative and hypnotic medications
- Avoid hormonal contraception and hormonal replacement therapy (under specialist advice only)
- Consider adherence issues with endocrine therapies and with the other regular medications. (It is estimated half of women prescribed endocrine therapy take their treatment less than 80% of the time)

USEFUL RESOURCES

ESMO expert consensus statements on cancer survivorship: promoting high-quality survivorship care and research in Europe

American Cancer Society/ASCO guideline on Cancer Survivorship for breast cancer patients

National Cancer Care Programme- Survivorship

HSE patient information- living with cancer

NICE guidelines on the management of breast cancer

ASCO guidelines on the management of menopausal symptoms, fertility preservation and bone health for women with breast cancer on endocrine therapy

Lancet Oncology paper 2021 on evidence-based approaches for the management of side-effects of adjuvant endocrine therapy in patients with breast cancer

The British Menopause Society statement on the management of oestrogen deficiency symptoms, arthralgia and menopause in women treated for early breast cancer

European Society of Cardiology 2022 guidelines on cardio-oncology

GP focused Osteoporosis guideline for men over the age of 50 and post-menopausal women

FSRH CEU guidance: supporting contraceptive choices for individuals who have or have had breast cancer

This is GO (link to supports for patients and information for HCWs)

LACES: Life and cancer; enhancing survivorship programme. (Irish Cancer Society)

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