Breast cancer accounts for one third of all newly diagnosed cancers in females in Ireland and is the second highest cause of cancer death.

Modern management of breast cancer involves a multidisciplinary approach including radiology, pathology, surgery, radiation and medical oncology input.

The choice of systemic therapy is determined by the stage and subtype of the tumour.

Patients require ongoing support to persist with treatment and to enable return to normal life activities.

INTRODUCTION

Breast cancer is the commonest tumour diagnosed in women in most areas of the world, especially in industrialised areas. In Europe, it accounts for 30% of all incident tumours in females. A recent report from the National Cancer Registry of Ireland (NCRI) showed that from 2007-2009 approximately 2,670 women were diagnosed with breast cancer annually in Ireland, equivalent to 33% of all cancers. While there has been a continuous decline in mortality during the last 20 years, breast cancer was the second leading cause of cancer death in Ireland during 2007-2009 (second only to lung cancer), accounting for 16% of all female cancer deaths. Ireland has the 4th highest breast cancer mortality rate of 30 European countries according to the European Cancer Observatory figures. The NCRI report documents that the mean age of women at time of diagnosis of breast cancer is 59.6 years underpinning the fact that breast cancer remains an important public health issue in Ireland.

The National Cancer Control Programme (NCCP) has seen significant changes in the structure and delivery of cancer services in Ireland, with the establishment of 8 designated cancer centres. This bulletin will outline the current management options for breast cancer in Ireland.

RISK FACTORS FOR BREAST CANCER

The major determinants of breast cancer risk relate to age and lifetime exposure to oestrogen: early menarche, nulliparity or low parity, late age at first pregnancy (>30 years), use of combined oral contraceptives, late natural menopause and use of hormone replacement therapy (HRT) are associated with an increased risk (<2-fold increase) of breast cancer. Environmental risk factors include smoking, alcohol and obesity (particularly in postmenopausal breast cancer). Prior benign breast disease is not in itself a risk factor unless “proliferative” changes have been noted on biopsy. Increased breast density, as assessed by mammography and reflecting breast tissue composition, has been associated with increased risk of breast cancer. Factors that have been associated with a reduced risk of breast cancer include: breast feeding, physical activity, greater body fat in the pre-menopausal phase and the use of drugs such as selective estrogen receptor modulators (SERM e.g. raloxifene). Less than 10% of breast cancers arise as a direct result of specific genetic mutations, the most frequently associated genes are BRCA1 and BRCA2.

DIAGNOSIS AND CLASSIFICATION OF BREAST CANCER

The diagnosis of breast cancer in Ireland is either via the National Screening Programme (BreastCheck) or symptomatic breast clinics in any of the designated cancer centres, where women with suspicious symptoms or signs are assessed. The standard assessment of a suspicious breast symptom is Triple Assessment i.e. clinical examination, radiological investigations (mammography +/- ultrasound) and histological reporting of biopsies of suspicious abnormalities detected on physical examination or via radiology. Following a diagnosis of breast cancer, each case is individually discussed at a multidisciplinary team (MDT) meeting (involving surgeons, radiologists, pathologists, radiation oncologists and medical oncologists) to ensure the best line of treatment is recommended for each individual.

Breast cancer comprises a heterogeneous group of diseases. The introduction of screening programmes has led to the increased detection of “ductal carcinoma in situ” (DCIS) which is a pre-malignant condition. As the focus of this bulletin is breast cancer, further information on DCIS will not be presented. Breast cancer can be classified according to tissue origin i.e. ductal or lobular; immunohistochemical receptor status i.e. hormone positive or negative, HER2 positive or negative or triple negative (hormone oestrogen/progesterone and HER2 receptor negative) or on the basis of genomic profiling i.e. luminal A and B, HER2, basal-like or normal subtypes. These subtypes have prognostic (i.e. relating to outcomes) and predictive (i.e. predicting response to treatment) implications.

TREATMENT OF BREAST CANCER

Management of breast cancer is undertaken by a MDT. Studies have shown improved survival with use of such teams. There are several established staging systems described, but essentially patients may have early (i.e. confined to the breast +/- axilla), locally advanced (i.e. large or fungating tumour in the breast +/- extensive local nodal involvement) or metastatic (metastases in distant organs) disease. Therefore, the tumour is staged according to whether the disease is confined to within the breast (i.e. local) or spread to the local lymph nodes in the axilla (regional), or is metastatic (metastases found in other/distant areas of the body).

MANAGEMENT OPTIONS IN NON-METASTATIC BREAST CANCER

Surgery

The main surgical options are mastectomy or breast conserving surgery followed by radiation therapy. Approximately 2/3 of newly diagnosed cancers are amenable to breast conservation which consists of wide local excision followed by radiotherapy. Mastectomy is recommended for patients with large tumour size (>5 cm in diameter), tumour multifocality, prior radiation to the chest wall or breast, in the setting of patient preference and in the infrequent setting of pregnancy-related breast cancer. Breast reconstruction is an option for women who have undergone mastectomy; there is no evidence that reconstruction makes detection of local recurrence more difficult. The timing of reconstruction is discussed with the patient, surgeon and radiation oncologist.
Axillary surgical options include sentinel node excision, axillary sampling or axillary clearance. These decisions are made by the MDT. The presence of **regional lymph node involvement is a strong predictor of long-term prognosis in early breast cancer**. The risk of upper limb lymphoedema post-surgery ranges from 3–40% depending on the extent of axillary node removal.10

**Radiotherapy**

Breast radiotherapy is **recommended after breast conservation surgery**, as it reduces by 2/3 the risk of local recurrence. Radiation post-mastectomy may be indicated for patients with >4 axillary nodes or for those with large primary tumours and is discussed at the MDT meeting.10 The other indication for the use of radiation therapy is in the setting of metastatic disease, where it is used for palliation in the control of bone or brain metastases.11

**Systemic Therapy**

Systemic therapy refers to the use of orally or parenterally administered anti-cancer therapies, including endocrine (hormonal) therapy, chemotherapy or HER2 directed therapy. The two scenarios are a) adjuvant i.e. following surgery where the patient has no documented metastatic disease and the intent is to reduce the risk of developing recurrent or metastatic breast cancer or b) metastatic where the use is palliative, to control the disease. Use is determined by the molecular profile of the tumour as follows;14

**Endocrine therapies**: These agents reduce the risk of recurrence of hormone-positive (+ve) breast cancer, the most commonly occurring type of breast cancer.15 Table 1 outlines the currently available agents.

**Chemotherapy**: Chemotherapeutic agents are used primarily in patients with 1) high risk disease (node positive, young age), 2) hormone receptor negative (-ve) tumours, 3) HER2+ve tumours and 4) triple negative tumours.5,10,25 They may also be used in association with endocrine therapy for some tumour types [see below]. In general, these “cytotoxic” agents, act by interfering with rapidly dividing cancer cells.26

They are usually given in combination (as polychemotherapy) to improve efficacy and reduce toxicity and are administered

**Table 1: Endocrine therapies for breast cancer treatment**

<table>
<thead>
<tr>
<th>Class</th>
<th>Agents in Class</th>
<th>Mode of Action</th>
<th>Setting</th>
<th>Side effects / Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>SERM</td>
<td>Tamoxifen</td>
<td>Anti-oestrogenic effects in breast cancer</td>
<td>Adjuvant or Metastatic</td>
<td>Early menopause, hot flushes, fluid retention, vaginal bleeding, uterine cancer, VTE. CYP 2D6 inhibitors may ↓ efficacy. ADRs as above. Only for PM Patients. Not affected by CYP2D6 inhibitors.</td>
</tr>
<tr>
<td></td>
<td>Toremifene</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aromatase inhibitor (AI)</td>
<td>Anastrozole</td>
<td>Prevents production of oestradiol</td>
<td>Adjuvant or Metastatic</td>
<td>Hot flushes, arthralgia, vaginal bleeding. ↑ risk of fracture due to ↓ bone mineral density. Only for PM patients ADRs as per other AIs. Only for PM patients</td>
</tr>
<tr>
<td></td>
<td>Letrozole</td>
<td></td>
<td>Adjuvant or Metastatic</td>
<td>ADRs as per other AIs. Only for PM patients</td>
</tr>
<tr>
<td></td>
<td>Exemestane</td>
<td></td>
<td>Adjuvant or Metastatic</td>
<td>ADRs as per other AIs. Only for PM patients</td>
</tr>
<tr>
<td>LHRH analogue</td>
<td>Goserelin*</td>
<td>Inhibits pituitary LH secretion leading to reduced oestradiol levels</td>
<td>Adjuvant or Metastatic</td>
<td>Hot flushes, arthralgia, bone pain, ↓ bone mineral density, weight gain. Use in pre- + peri-menopausal patients</td>
</tr>
<tr>
<td>Progestin</td>
<td>Megestrol acetate</td>
<td>Anti-oestrogenic effects</td>
<td>Metastatic</td>
<td>May cause weight gain, hot flushes, VTE, breakthrough bleeding</td>
</tr>
<tr>
<td>Competitive ER antagonist</td>
<td>Fulvestrant*</td>
<td>Anti-oestrogenic effects</td>
<td>Metastatic</td>
<td>Soreness at injection site, hot flushes. Only for PM patients</td>
</tr>
</tbody>
</table>

*administered by monthly injection; SERM= selective oestrogenic receptor modulator; ER= oestrogen receptor; PM = post-menopausal; ADR = adverse drug reaction; LHRH = luteinising hormone releasing hormone; VTE = venous thrombo-embolism

Endocrine therapies work by reducing oestrogen levels / effects in the body. **Tamoxifen** has been used for over 4 decades and is effective in both the pre- and post-menopausal setting. Results from 15-years’ follow-up of 129 breast cancer treatment randomised controlled trials have documented that, **in patients with hormone receptor+ve disease, use of adjuvant tamoxifen for 5 years reduces the annual breast cancer death rate by 31% , irrespective of age, menopausal status, or other tumour characteristics and irrespective of the use of chemotherapy.**13 Side effects include hot flushes, fluid retention, vaginal bleeding, endometrial fibroids, endometrial cancer and thromboembolic events (Table 1).16 There is a **potential for reduced tamoxifen efficacy in the presence of reduced CYP2D6 activity**, due to lack of formation of the active metabolites; therefore concomitant use of moderate CYP2D6 inhibiting drugs such as some SSRIs (e.g. paroxetine and fluoxetine) is not recommended.24 Since a number of SSRIs (e.g. citalopram, escitalopram, sertraline) have minimal / dose-related effects on CYP2D6, it would seem prudent to use an alternative SSRI to paroxetine and fluoxetine where possible. The SNRI venlafaxine has a low potential for affecting CYP2D6, and may provide an alternative option in some cases.24 **Optimal duration of tamoxifen use is five years.**15

**Aromatase inhibitors (AI)**, which block the formation of oestradiol are licensed for use in the post-menopausal setting; numerous studies have shown similar 5-year survival to tamoxifen but slightly lower recurrence rates in the adjuvant setting.13,35 They are not used in pre-menopausal patients because a functioning ovary may be able to produce additional amounts of aromatase to bypass the inhibition.20,21 These agents do not have the risks of thrombo-embolism or endometrial cancers reported with tamoxifen, but are associated with arthralgia / joint stiffness, vaginal bleeding and hot flushes.20 They also cause a reduction in bone mineral density resulting in increased risk of osteoporosis and fracture. **Recommended duration of use currently is five years.**20 There are many studies underway in the post-menopausal setting attempting to identify the optimal duration of use of endocrine therapy and the optimal sequence of their use.14

Reversible ovarian ablation is achieved with use of **LHRH analogues**; this treatment option may be useful in pre- and peri-menopausal patients.19 **Optimum duration of treatment with LHRH analogues has not been established but current guidance recommends that they should be used for at least 2 years.**1 These agents must be administered by monthly injection, which may limit patient acceptability.19

**Chemotherapy**: Chemotherapeutic agents are used primarily in patients with 1) high risk disease (node positive, young age), 2) hormone receptor negative (-ve) tumours, 3) HER2+ve tumours and 4) triple negative tumours.5,10,25 They may also be used in association with endocrine therapy for some tumour types [see below]. In general, these “cytotoxic” agents, act by interfering with rapidly dividing cancer cells.26
Clinical trials have demonstrated that *chemotherapy regimens containing an anthracycline and/or a taxane are associated with improved outcome*, compared with older regimens such as CMF (see Table 2), especially in patients with axillary node involvement at time of diagnosis.\(^{14,15}\) The choice of combination, recommended for use by the medical oncologist is based on tumour factors (size, grade, axillary nodal status, hormone receptor status and HER2 status) as well as patient factors (performance status, co-morbidities and prior chemotherapy).\(^{5,10,13}\) Age is not a contraindication to the use of polychemotherapy, however older patients (>70 years) are poorly represented in chemotherapy clinical trials.\(^{15}\) Moreover, follow-up data from clinical trials show that the absolute benefits at 10 or 15 years appear to be about 3 times as great for younger women (<50 yrs) than for older women, with the benefits being greater for recurrence than for mortality.\(^{15}\)

**HER2 directed therapy:** HER2 (human epidermal growth factor receptor 2) positivity or over-expression is seen in approximately 20% of newly diagnosed breast cancers and has historically been considered an adverse prognostic factor in breast cancer, associated with a higher (and early) risk of recurrence, and with a relative resistance to established chemotherapeutic regimens such as CMF (see Table 2).\(^{14}\) **Trastuzumab** is a monoclonal antibody which binds to the HER2 receptor and inhibits proliferation of human tumour cells that over-express HER2.\(^{10}\) Use of trastuzumab, either in combination with or subsequent to chemotherapy, has shown improvement in response rates and overall survival compared with chemotherapy alone in patients with HER2+ve breast cancer.\(^{10,14,16}\) Current guidelines recommend one year of therapy.\(^{10}\) **Trastuzumab is associated with cardiotoxicity**, with 2-4% of patients experiencing symptomatic heart failure; therefore patients who are being considered for trastuzumab treatment should have a thorough baseline cardiac assessment performed. During treatment, cardiac function is generally assessed every 12 weeks and treatment discontinued if the benefits of trastuzumab are outweighed by the development of heart failure.\(^{10}\) **Concomitant use with an anthracycline is not recommended.** **Lapatinib** is another HER2 targeted therapy, which has shown benefit (in combination with other systemic therapies) in HER2+ve breast cancer patients in the advanced or metastatic disease setting.\(^{37,38}\)

**DIAGNOSIS AND MANAGEMENT OF BREAST CANCER IN PRACTICE**

Earlier detection of breast cancer is associated with improved survival. BreastCheck, which screens women of 50-64 years, has resulted in increased detection rates as a result of detecting small non-palpable lesions.\(^2\) However, many breast cancers are diagnosed via clinical examination regardless of age.

**EARLY BREAST CANCER**

Once a histological diagnosis is made, the patient’s treatment pathway is decided by the MDT. Treatment will target the tumour at local level (i.e. surgery +/- radiotherapy) to remove the primary tumour. **Most early breast cancer patients also receive some form of systemic therapy to reduce the risk of cancer recurrence.**\(^{10}\)

**Adjuvant Systemic Therapy** is administered, post-surgery.\(^{10}\) It aims to eradicate undetectable micrometastatic deposits of tumour that may be present at the time of diagnosis.\(^{14}\) Table 3 outlines adjuvant treatment approaches according to tumour hormone receptor and HER2 expression status.

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### Table 2: Commonly used chemotherapeutic agents and regimens in breast cancer patients\(^{26-35}\)

<table>
<thead>
<tr>
<th>Drug Class (Mode of Action)</th>
<th>Agent(s) in Class</th>
<th>Treatment Regimen(s)*</th>
<th>Comments on specific adverse drug reactions**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines (anti-DNA action)</td>
<td>Doxorubicin (A); Epirubicin (E)</td>
<td>AC; CAF; CEF; DAC</td>
<td>May cause irreversible cardiomyopathy (related to total drug dose)</td>
</tr>
<tr>
<td>Taxanes (inhibits cell division)</td>
<td>Docetaxel (D); Paclitaxel</td>
<td>DAC</td>
<td>May cause severe hand + foot syndrome (bullous eruptions), cardiotoxicity</td>
</tr>
<tr>
<td>Alkylating agents (interfere with DNA synthesis)</td>
<td>Cyclophosphamide(C)</td>
<td>CMF; DAC; CAF; CEF</td>
<td>May be associated with haemorrhagic cystitis</td>
</tr>
<tr>
<td>Pyrimidine analogues (inhibits DNA synthesis)</td>
<td>5-Fluorouracil (F); Capecitabine</td>
<td>CMF; CAF; CEF</td>
<td>Commonly causes GI disturbance</td>
</tr>
<tr>
<td>Folic acid analogues (inhibits DNA synthesis)</td>
<td>Methotrexate (M)</td>
<td>CMF</td>
<td>May cause ulcerative stomatitis</td>
</tr>
</tbody>
</table>

* usually >4 cycles of therapy are given and patients may be treated with two sequential regimens

**bone marrow suppression occurs with majority of agents and most are associated with alopecia and mucus membrane toxicity with associated GI disturbance

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The laboratory test **OncoType DX®** may be used to determine whether a woman with hormone receptor+ve, HER2-ve, lymph node negative primary breast cancer requires chemotherapy in addition to adjuvant endocrine therapy.\(^{39,40}\) The test generates a Recurrence Score®, quantifying the likelihood of breast cancer distant recurrence into: low-risk, intermediate-risk and high-risk. Clinical data published for the use of OncoType DX® have shown that up to 30% of women who would otherwise have received chemotherapy will now be considered as low risk, requiring the use of endocrine therapy alone.\(^{39}\)
Neoadjuvant (Primary) Systemic Therapy describes the administration of systemic therapy prior to surgery at initial diagnosis in order to reduce the tumour size to facilitate subsequent surgery. It is indicated for large tumours, inflammatory breast cancer (a particularly aggressive form of breast cancer) and for those tumours with local or regional spread. The choice of systemic therapy for patients requiring neoadjuvant therapy, is also based on the hormone receptor / HER2 status (as per Table 3).

METASTATIC BREAST CANCER (MBC)
The majority of MBC presents as a recurrence of previously treated primary breast cancer although it can occur at the first presentation of a malignant breast mass (<10% of cases). The aim of management is prolongation of life, control of tumour burden and symptoms and maintenance of quality of life (QoL) and the principles of therapy are along those for any chronic disease. Therapy is not generally considered curative. Systemic therapy is administered according to hormone receptor / HER2 status (see Table 3) and patient performance status. In addition, patients with MBC who have bony metastases are generally also commenced on bisphosphonates, which have been shown to ease pain and reduce the risk of fracture at the site. Radiotherapy may also be used in the palliative management of troublesome bone or brain metastases.

SUPPORTIVE MEDICAL CARE
Chemotherapy-induced nausea and vomiting are common (see Table 2) and radiotherapy may also induce similar toxicity. These symptoms add to the distress for patients; current guidelines recommend that patients, receiving combination chemotherapy and radiotherapy, should be routinely treated with anti-emetic therapy according to the recognised degree of emetic risk. Symptom control is monitored throughout therapy and anti-emetic therapy modified as required. Endocrine therapy-associated adverse effects (see Table 1) should be proactively managed to maintain the patient’s QoL and promote adherence to the treatment regimen given that they are generally prescribed for at least five years. Studies have shown that adverse effects, due to reduction in circulation levels of oestrogen (menopausal symptoms), may be particularly troublesome for both pre- and post-menopausal patients in the early phase of treatment, with QoL improving with longer therapy duration. Patients receiving AI therapy should be given vitamin D and calcium supplementation because of the risk of accelerated bone loss and osteoporosis, and patients receiving tamoxifen should be monitored for abnormal uterine bleeding.

FOLLOW-UP CARE FOR BREAST CANCER PATIENTS
Surveillance, following a diagnosis of breast cancer involves the 1) management of treatment-related complications, 2) early detection of recurrence or contralateral breast cancer and 3) provision of psychological support and information to aid persistence with treatment and to promote return to normal life activities. History and physical examinations are generally performed every 3 - 6 months for the first 3 years, every 6 - 12 months for years 4 and 5, and annually thereafter. Unless otherwise indicated, a yearly mammographic evaluation should be performed. Routine radiological examinations (e.g. CTs, MRI, bone scans) and blood tests (e.g. FBC, bone profile, tumour markers) are not recommended in asymptomatic patients.

BREAST CANCER AND PREGNANCY
Breast cancer arising during pregnancy is uncommon (estimated to occur in 1:1,000 pregnancies). The characteristics of breast cancer during pregnancy are similar to that for a non-pregnant woman of similar age and the treatment pathway is similar, although there are problems with the use of radiology for staging and use of certain systemic therapies, especially during the first trimester. Surgery can be performed at any stage of diagnosis. The aim of the MDT (with the inclusion of the obstetrician) is to optimise outcome for both mother and child.

CANCER SURVIVORSHIP
A cancer survivor is any person who has received a diagnosis of cancer, from the time of diagnosis throughout his/her life. Cancer survivors face a myriad of long-term physical, psychosocial and financial effects from their cancer diagnosis and treatment. In addition they have a greater risk for new cancers compared with individuals who have never had cancer. Various health lifestyle behaviours have been shown to prevent or reduce cancer development / recurrence, including physical activity, no cigarette smoking, and maintaining a normal weight. Research has shown that breast cancer survivors may experience clinically relevant distress up to 48 months post diagnosis. It is important that healthcare professionals dealing with cancer survivors encourage a healthy lifestyle and recognise possible stress in order to intervene in terms of education or social support mechanisms. The Irish Cancer Society has a wide range of counselling and other practical services for cancer survivors (check out http://www.cancer.ie/how-we-can-help).

SUMMARY POINTS
- Early detection of breast cancer improves prognosis. The NCCP operates a rapid referral system to symptomatic breast clinics for GPs in Ireland. Forms available at: http://www.hse.ie/eng/services/Find_a_Service/National_Cancer_Control_Programme/
- All breast cancers are managed by a multidisciplinary approach involving surgery, radiotherapy and systemic therapy
- The choice of systemic therapy depends on the extent of the cancer and on the presence or absence of hormone receptors / HER2 over-expression
- Chemotherapy lasts for approximately 3-5 months, HER2 directed therapy for one year and endocrine therapy for at least 5 years.
- Patients should be supported to persist with the recommended duration of treatment to ensure optimal benefit in terms of improved survival
- The promotion of a healthy lifestyle and reduction of stress-related symptoms will improve overall survival in cancer survivors. Patient support is available at: www.cancer.ie
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