

Treatment of early breast cancer

In a second article on breast cancer, **Sandra Melville** and **Lucy Heycock** give an insight into the use of chemotherapy, hormonal therapy and the monoclonal antibody trastuzumab, and describe how these fit in to an overall breast cancer treatment plan

Although the incidence of breast cancer is increasing, screening programmes and developments in pharmacological therapies have caused mortality rates to drop. In cancer centres, pharmacists are becoming key players in the management of breast cancer patients, with an increasing number undertaking prescribing roles. However, by being aware of the challenges that these patients face, and having an understanding of the mechanisms underlying the toxicities associated with treatment, community pharmacists can offer a valuable, proactive and much needed service.

Neoadjuvant therapy

Treatment that aims to shrink large tumours before surgery is called neoadjuvant therapy. With regard to breast cancer, this can include chemotherapy and hormonal therapy.

Neoadjuvant chemotherapy Cytotoxic drugs work by different mechanisms but all interfere with cell replication. Chemotherapy regimens usually consist of two or three agents, each obstructing a different stage of the replication process. Normal cells are affected as well as cancer cells so chemotherapy must be given in cycles to allow them to recover. Doxorubicin plus cyclophosphamide (AC) has been used in combination as neoadjuvant treatment, although vinorelbine with epirubicin has been found to be as least as effective, with less severe nausea, vomiting and alopecia. More recently, the addition of a taxane to AC has been shown to shrink tumours more effectively.

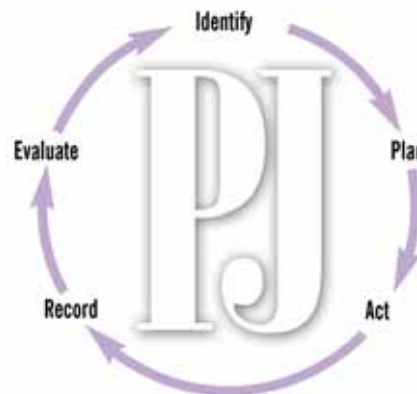
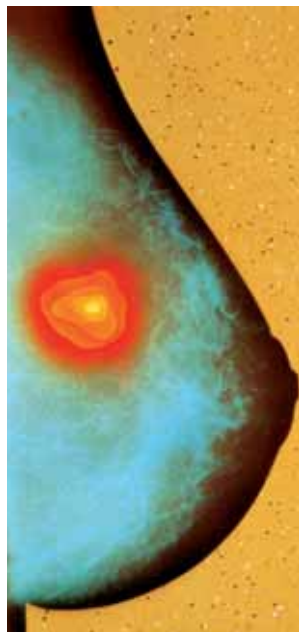
In addition to shrinking large tumours to allow more effective surgery, neoadjuvant chemotherapy can also be given to a small number of patients whose tumour is inoperable but not metastatic at presentation.

Neoadjuvant hormonal therapy

Occasionally tamoxifen can be prescribed for up to six months before surgery. More recently, however, the aromatase inhibitor letrozole has been used with good results — patients were less likely to require a total mastectomy than those receiving tamoxifen.

Surgery

Surgery is usually the first-line treatment. Two well-established, surgical procedures for local treatment of invasive breast cancer are mastectomy (removal of the whole breast) and conservation surgery (where the tumour and a margin of surrounding normal tissue are excised). Conservation surgery (also described as “lumpectomy” or “segmentectomy”) accounts for over half of early stage breast cancers and can range from wide local



Identify knowledge gaps

1. What are the treatment options for breast cancer?
2. What are the main side effects of treatment?
3. What are the latest developments in the pharmacological management of breast cancer?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in “Plan and record”, (available at: www.rpsgb.org/education). This article relates to “common disease states” (see appendix 4 of “Plan and record”).

incision, whereby the tumour is removed with some surrounding tissue, to a quadrantectomy in which about a quarter of the breast is removed. Mastectomy may be considered the best option when the tumour is in the centre of the breast or directly behind the nipple, the breast is small and may be distorted by partial mastectomy or when there are several cancerous or pre-cancerous areas.

Spread of the cancer to axillary nodes is the most significant prognostic indicator and knowledge of this is vital for selecting the best systemic adjuvant treatment (see later). Patients will also, therefore, undergo axillary node sampling, where a few lymph nodes are taken from the axillary fat. Newer techniques, such as sentinel lymph node biopsy, are being introduced as an alternative, reducing the unnecessary removal of nodes. For cancers that have spread to the axillary nodes, axillary surgery will be carried out.

Side effects of these operations include temporary swelling, tenderness and hardness due to scar tissue. The main side effect of removing axillary lymph nodes is lymphoedema, which is experienced by up to 30 per cent of patients. This is characterised by swelling, tightness or pain in the arm. Patients experiencing these symptoms should seek advice and treatment (eg, physiotherapy). Wound infection, accumu-

Sandra Melville, BSc, MRPharmS, is clinical pharmacist at Lorn & Islands District General Hospital, Oban, Argyll, and **Lucy Heycock, MSc (cancer nursing)**, is a Macmillan nurse specialist

lation of blood in the wound (haematoma) and accumulation of clear fluid in the wound (seroma) can also occur.

Patients will be encouraged to exercise as soon as possible after surgery to help them regain normal arm movements. In addition, exercise can promote tissue healing because more oxygen is supplied to the area. Instructions and advice on appropriate exercises will be given by the treatment centre.

Women who are to undergo a mastectomy will usually be offered breast reconstruction. This can be carried out with the mastectomy or later. An implant can be used to replace breast tissue or a new breast can be constructed from the woman's abdominal or back muscles, or a combination of both techniques can be used.

Adjuvant therapy

After surgery, most patients will be advised to have therapy to reduce the risk of recurrence or metastatic disease. This is known as adjuvant therapy.

Adjuvant chemotherapy If appropriate, (ie, in patients with a Nottingham prognostic index of 3.4 or higher [see *PJ*, 15 September, pp299–301]) adjuvant chemotherapy is usually started within six weeks of surgery and is generally given for six to seven months. Examples of chemotherapy regimens are given in Panel 1. The value of adjuvant chemotherapy in breast cancer was first fully appreciated in 1976 when Bondadonna *et al* published their study, which also launched the most well-known chemotherapy regimen, CMF (cyclophosphamide, methotrexate and fluorouracil). Since then, many variations of this classic regimen have been used and studies have shown that the addition of an anthracycline improves outcomes. Earlier studies used doxorubicin but it is now well recognised that epirubicin has a better cardiotoxicity threshold, giving the potential for higher doses of the anthracycline component.¹ This regimen (EPI/CMF) is used today.

More recently taxanes have been introduced to adjuvant regimens. The National Institute for Health and Clinical Excellence has recommended docetaxel, as part of the TAC (docetaxel, doxorubicin, cyclophosphamide) regimen for women with early node-positive breast cancer.² However, it has not recommended the use of paclitaxel as adjuvant treatment for these patients, possibly because efficacy has only been demonstrated when used with AC.³ AC is thought to be less effective than the two more commonly used regimens, FEC and EPI/CMF and NICE was not convinced that AC followed by paclitaxel offered a better outcome. However, the guidance is due to be reviewed.

Because cytotoxic agents have such a narrow therapeutic index, chemotherapy doses are generally calculated using body surface area (BSA) rather than weight. BSA may be determined from height and weight using a formula or nomogram. (The electronic version of the British National Formulary has

Panel 1: Adjuvant chemotherapy regimens

EPI/CMF Epirubicin 100mg/m² on day 1 and repeated every 21 days for four cycles. Followed by CMF (cyclophosphamide 600mg/m² IV, methotrexate 40mg/m² IV plus fluorouracil 600mg/m² IV) on days 1 and 8 and repeated every 28 days for four cycles.

FEC Fluorouracil 600mg/m² IV, plus epirubicin 60mg/m² IV plus cyclophosphamide 600mg/m² IV, on day 1 and repeated every 21 days for six cycles.

AC Doxorubicin 60mg/m² IV, plus cyclophosphamide 600mg/m² IV, on day 1 and repeated every 21 days for four cycles.

Panel 2: Interventions to help prevent or relieve chemotherapy side effects

Nausea Once nausea becomes established it can be difficult to address. Prophylactic anti-emetics (eg, domperidone or metoclopramide plus dexamethasone) are, therefore, normally given with chemotherapy. A 5HT₃ antagonist (eg, granisetron or ondansetron) may be added, depending on the emetogenicity of the regimen and the susceptibility of the patient. Lorazepam has been shown to help anticipatory nausea, which can become a problem if untreated. More recently, the neurokinin receptor antagonist aprepitant has been licensed as an adjunct to dexamethasone and a 5HT₃ antagonist for the prevention of chemotherapy induced nausea and vomiting. Eating smaller meals more frequently and avoiding constipation (a side effect of 5HT₃ antagonists) can be helpful.

Alopecia For many women alopecia is the most difficult side effect to deal with and, unfortunately, there is no pharmaceutical remedy. Scalp-cooling (where a cool, gel-filled cap is placed over the scalp before chemotherapy) is used in some centres. This reduces blood flow to the scalp, which, in turn, should reduce the amount of cytotoxic reaching hair follicles, but reports of effectiveness vary.

Oral mucositis Good oral hygiene is important to prevent oral mucositis. Antiseptic mouthwashes (eg, chlorhexidine) or a simple sodium bicarbonate mouthwash can be helpful. If ulcers develop, preparations such as Adcortyl in Orabase or Corlan pellets may be useful, but because patients are immunocompromised it is always worth first checking for candidal infection.



Lymphoedema is characterised by swelling, tightness or pain in the arm

the facility to do this calculation if a patient's height and weight are entered.)

Cancer cells tend to replicate faster than normal cells so they are affected more by cytotoxic agents. Similarly, healthy cells that divide rapidly (eg, those found in the gastrointestinal tract, bone marrow and hair follicles) are more prone to the effect of cytotoxics. Not surprisingly, the main side effects of chemotherapy are nausea and vomiting, myelosuppression and alopecia. Other common side effects include mucositis, cardiotoxicity, renal toxicity and neutropenia. Each can be distressing and, indeed, debilitating if not treated adequately. Neutropenic sepsis is a side effect that can occur when blood counts are at their lowest (generally around 10 days after chemotherapy). It can be fatal if not treated with intravenous antibiotics and patients with influenza-like symptoms should be advised to contact their GP or cancer centre immediately.

Pharmacists can support patients undergoing chemotherapy by watching out for side effects and providing advice. Panel 2 describes some interventions to help prevent or relieve chemotherapy side effects.

Adjuvant hormonal therapy Oestrogen is the main hormone involved in the devel-

Panel 3: Guidelines for adjuvant hormonal therapy*

Factors	Treatment
Very low risk (Nottingham prognostic index < 3.4 and no nodes)	Tamoxifen alone for five years
All Her2+ All ER+ and PR- Grade 3 plus four nodes or more and not having chemotherapy Contraindication to tamoxifen	Immediate anastrozole or letrozole for five years
Grade 3 plus four nodes or more and having chemotherapy Her2- and PR+ †	Switch to exemestane or anastrozole after 2.5 years of tamoxifen to complete five years
All other breast cancers	Switch to letrozole for three years after five years of tamoxifen

* Adapted from WOSCAN Breast Cancer Managed Care Network guidelines for adjuvant use of aromatase inhibitors

† Using Her2 and PR status to guide use of AIs is not universally accepted because trial evidence is either weak or contradictory

Panel 4: Basic radiotherapy skin care guidelines*

- Perfumed products (eg soap, perfume, deodorant) can cause skin soreness.
- Avoid friction: pat rather than rub skin dry and wear loose, natural fibre clothing.
- Do not shave, wax or use hair removing cream on the irradiated site.
- Patients can swim once the redness has settled down but chlorine in swimming pools can have drying effect on skin
- Avoid direct application of heat or cold to area (eg, gels, creams or lotions should not be refrigerated).
- The treated area can be sensitive to sunlight for up to a year. Avoid sun exposure and use sunblock of at least SPF 15.

* Adapted from NHS Quality Improvement Scotland, Best Practice Statement 2004

opment and growth of breast tumours. However, hormonal therapies are only effective in patients whose cancer cells have surface receptors for oestrogen or progesterone, or both. This is known as being oestrogen receptor positive (ER+) or progesterone-receptor positive (PR+). ER+ and PR+ tumours tend to grow less aggressively, resulting in a better prognosis.

All patients who are ER+ should receive hormonal therapy. The aim is to deprive cancer cells of oestrogen. This is achieved either by blocking oestrogen receptors on tumour cells (eg, tamoxifen) or reducing the amount of circulating oestrogenic compounds. Treatment differs for pre- and post-menopausal women. Pre-menopausal women who are ER+ or PR+ are usually given tamoxifen 20mg *od* for five years, starting four weeks after surgery or, for those who have had adjuvant chemotherapy, three or four weeks after the chemotherapy is completed — chemotherapy and tamoxifen should not be given concurrently. Patients taking tamoxifen should be made aware of the side effects, particularly the risk of thromboembolism and endometrial cancer, but should be reassured that the benefits of treatment outweigh the risks.

Post-menopausal women who are ER+ or PR+ can also be prescribed tamoxifen but the past few years have seen many trials of aromatase inhibitors (AIs) and an increase in

the licensed indications for each. AIs block the conversion of androgens to oestrogens in peripheral tissues. They do not inhibit ovarian oestrogen synthesis and are not, therefore, indicated in pre-menopausal women. NICE published guidelines in 2006, which recommend the use of anastrozole, letrozole and exemestane as options for adjuvant treatment of early ER+ invasive breast cancer in post-menopausal women.

Although significant improvements in disease-free survival have been demonstrated, only one sub-group (node positive) of one AI trial (MA-17) has, so far, shown an overall survival benefit. Lack of evidence makes it difficult to choose between AIs but taking toxicity, effectiveness, risk of recurrence and regulatory status into account, the West of Scotland Cancer Network's Breast Cancer Managed Care Network has drawn up guidelines for their use (see Panel 3).

Side effects of AIs include muscular and joint pains, osteoporosis, fractures, vaginal dryness and loss of libido. All AIs reduce bone mineral density (due to oestrogen lowering) and their summaries of product characteristics include a warning that women with osteoporosis, or who are deemed to be at risk of osteoporosis, should have their bone mineral density assessed by bone densitometry at the beginning of treatment (and for anastrozole at regular intervals thereafter). Treatment or prophylaxis of osteoporosis (with calcium and vitamin D) should be initiated as appropriate.

Adjuvant radiotherapy The risk of recurrence of breast cancer can be reduced by 30 per cent by the addition of radiotherapy to surgery and systemic treatments. It is usually given after any type of partial mastectomy and also sometimes after a mastectomy. For those prescribed adjuvant chemotherapy, radiotherapy is given afterwards. It can be given at the same time as hormonal therapy.

Radiotherapy is restricted to specialist centres. It is a complex process and a number of steps are required between the decision to treat with radiotherapy and the first treatment. Before starting, patients have to attend one or two planning sessions in a simulator, where the area to be irradiated is measured and marked. Treatment plans vary but, generally, patients attend the radiotherapy unit five days a week for three to six weeks. The treatment itself usually takes 15 to 30 minutes.

Radiotherapy produces an inflammatory response and all patients are at risk of radiobiological skin damage. This affects skin regeneration and repair, and usually manifests 10 to 14 days into treatment. Reactions can range from itching, soreness and a feeling like sunburn to moist desquamation, and can continue to worsen for about 10 days after therapy, sometimes taking several weeks to resolve.

Whether or not a skin reaction develops depends on the dose of radiation and skin type. Some patients will have little or no reaction and those who do can usually be treated with simple moisturisers. When more severe sunburn-type reactions occur, treatment may

Pharmacists can support patients undergoing chemotherapy by watching out for side effects and providing advice

be delayed to give the skin time to heal. Silver sulfadiazine (Flamazine) cream may be useful.

Radiotherapy can also cause long-term changes to skin. A previously irradiated site can lose pigmentation, become indented (due to fibrosis of collagen and supporting structures in the dermis) and, occasionally, develop spidery red broken veins (telangiectasia). Fibrotic changes can also mean that the area will be permanently prone to poor healing.

Advice about skin care will be given by staff in the radiotherapy treatment centres, but because skin reactions persist after treatment it is important that local health care providers can provide a continuation of that care and advice (see Panel 4, p359).

Tiredness is another common side effect of radiotherapy. It can accumulate over the treatment period, and can have a significant impact on quality of life, lasting for a few weeks or even months after completion of treatment. Some clinics suggest that vitamin supplements may help.

Patients treated with some chemotherapy agents and who have had radiotherapy to treat a previous cancer may experience "radiation recall", an inflammatory reaction throughout the previously irradiated area.

Trastuzumab Trastuzumab is given by intravenous infusion every three weeks for one year or until routine computed tomography scans detect metastases. It is used after surgery, chemotherapy and radiotherapy (as appropriate). Human epidermal growth factor occurs naturally in the body. When it attaches itself to HER2 receptors on cancer cells, it stimulates them to divide and grow. The exact mechanism of actions for trastuzumab are unclear, but it is thought to work by attaching to HER2 (human epidermal growth factor 2) receptors, slowing down growth. Some breast cancer cells have more HER2 receptors than others (described as being HER2-positive). These grow more quickly than HER2-negative tumours, giving a poorer prognosis. It is thought that trastuzumab also sensitises cells to the effects of chemotherapy and perhaps the body's own immune system.

Patients who are HER2-negative will not gain any significant benefit from trastuzumab therapy. The 2006 NICE technology appraisal of trastuzumab as adjuvant therapy for early stage HER2+ breast cancer was based mainly on the results of the HERA study.⁴ This showed a 46 per cent relative reduction in recurrence risk and a 24 per cent relative reduction in one-year mortality.

The main side effect of trastuzumab is cardiotoxicity and cardiac function should be assessed before treatment and during therapy. Treatment should be stopped if left-ventricular ejection fraction drops by 10 per cent from baseline or to below 50 per cent. Trastuzumab should not be offered to women with an LVEF of 55 per cent or less.

Typical treatment pattern

Once a woman has been diagnosed with breast cancer she faces various treatment op-

Advanced breast cancer

Up to 30 per cent of patients will develop metastatic disease. Common sites for metastases include the liver, lungs, pleura, bones and brain. Prognosis will depend on various factors including age, extent of disease, hormone receptor status and HER2 status. If no treatment is given, the median survival from diagnosis of metastases is 12 months. However, with favourable factors, a woman may survive for 15 to 20 years. A short, disease-free interval suggests that recurrent disease will be resistant to adjuvant treatment. Hormonal treatment or chemotherapy will normally be the first-line treatments for metastatic disease. For patients who are HER2+, trastuzumab may be used alone or with chemotherapy. Bisphosphonates may be offered for patients with disease to the bone to relieve bone pain and prevent fractures.

tions, which may involve all or some of the following: surgery, chemotherapy, radiotherapy, hormonal therapy and trastuzumab. Surgery is usually the initial treatment. A woman is then likely to face six or seven months of chemotherapy followed by four or five weeks of radiotherapy. Depending on hormone receptor status, tamoxifen or an AI may also be prescribed. The treatment of breast cancer will take at least a year from the point of diagnosis (a further year if trastuzumab is indicated and five if tamoxifen is prescribed). Although many patients manage well with the treatment, some experience debilitating side effects. A knowledgeable and proactive local health care team can do much to support these women.

Future developments

The past two years have witnessed probably some of the most significant pharmacological advances in breast cancer, and trials into new agents are ongoing. The breast cancer vaccine lapuleucel-T (Neuvenge) is a product in a new class of active cellular immunotherapies, designed to stimulate a patient's own immune system to attack tumour cells. The vaccine is targeted against the HER2 antigen and activates T-cells, which may be the immune system's most potent defence against cancer. When activated to recognise tumour-associated antigens, T-cells proliferate and attack cells bearing those antigens. In phase I trials, patients typically received three infusions over a one-month period as a complete course of therapy.

References

1. Poole CJ, Earl HM, Dunn JA, Hiller L, Bathers S, Spooner D, et al. Phase III adjuvant breast trials show a significant relapse-free and overall survival advantage for sequential ECMF. *Proceedings of the American Society of Clinical Oncology* 2003;22:4 Abs 13.
2. Docetaxel for the adjuvant treatment of early node-positive breast cancer. Technology appraisal 109. London: National Institute for Health and Clinical Excellence; 2006.
3. Paclitaxel for the adjuvant treatment of early node-positive breast cancer. Technology appraisal 108. London: National Institute for Health and Clinical Excellence; 2006.
4. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *New England Journal of Medicine* 2005;353:1659-72.

Further reading

- Stanley A, Wright P, Allwood M. *The cytotoxics handbook*. Oxford: Radcliffe Publishing; 2001.

Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Visit www.breastcancer.org.uk and read the information about proactive side effect management (issue 9). What practical suggestions could you make to patients?
2. Think about how you would explain the unsuitability of trastuzumab to a HER2-patient, in light of recent media coverage.
3. Find a friendly patient on tamoxifen. Ask her about her treatment experiences and how pharmacists can provide support.

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions: What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?