Medical management of breast cancer

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Breast cancer remained the most common cancer in women in 2013 and its incidence continues to rise. Nonetheless, mortality is falling, partly as a result of earlier diagnosis through mammographic screening, improved surgical techniques and attention to margins, improved delivery of radiotherapy, and better adjuvant medical therapies (fig 1). Despite these improvements, breast cancer remains the second most common cause of death from cancer in women.

This review focuses on the medical treatment of breast cancer in the adjuvant and metastatic settings, with particular attention to recent advances and changes in practice since our last review in 2008. We discuss how targeted therapies can be used to individualise and tailor the management of breast cancer according to tumour biology and molecular subtype.

Early breast cancer

Diagnosis

Guidelines on the diagnosis of early breast cancer have changed little since our last review. Population based mammography screening for asymptomatic women is currently offered in the United Kingdom by the NHS Breast Screening Programme from age 47 to 73 years, with self referral encouraged thereafter. Women or men with breast symptoms are referred urgently to local specialist breast units (under the two week rule in the UK) for rapid assessment, including clinical assessment with mammography or ultrasound (or both) and biopsy as needed (triple assessment).

Local therapy

The breast

Surgical management aims to excise invasive and non-invasive cancer with clear margins. Breast conserving surgery followed by radiotherapy has equivalent survival to mastectomy. It should be offered if complete cancer excision can be achieved with adequate margins (>1 mm) and an acceptable cosmetic outcome. Mastectomy may be recommended when breast conserving surgery is not possible owing to tumour size, multifocal disease, aesthetically unfavourable ratio of breast size to tumour volume, or at the patient’s request. Primary medical (neoadjuvant) therapies are increasingly given before surgery to reduce tumour size and facilitate breast conservation.

The axilla

At the time that breast cancer is diagnosed, clinical staging of the ipsilateral axilla is achieved with axillary ultrasound and cytology or core biopsy of any suspicious lymph nodes. If the axilla is clinically negative, pathological axillary staging can be achieved with sentinel lymph node biopsy (SLNB), which is usually performed at the same time as breast surgery. In the past, axillary lymph node dissection (ALND) was recommended in patients with clinically positive nodes preoperatively and those who were positive at SLNB after a negative clinical assessment. The aim of ALND was to clear additional disease, maintain effective local disease control, and assess the total nodal disease burden as a way to accurately determine prognosis and the need for adjuvant therapies.

However, these two node positive groups of patients are very different with regard to disease burden; half of patients with a positive SLNB will have no further involved axillary lymph nodes on completion ALND performed after assessment of the sentinel lymph node. The Z0011 trial has questioned whether all SLN positive axillae require completion ALND. In this trial, more than 800 patients were randomised after breast conserving surgery and a positive SLNB (27% of whom had further involved lymph nodes) to either completion ALND or no further axillary surgery. Adjuvant therapies were offered according to pathological

SUMMARY POINTS

- Despite the increasing incidence of breast cancer, death rates are falling owing to earlier diagnosis, better surgical and radiotherapy techniques, and improved systemic therapies.
- The best management of the axilla in clinically node negative disease is unclear.
- Adjuvant decision making is driven by tumour biology, with particular attention to the distinct molecular subtypes of breast cancer.
- There is substantial evidence for extended hormone therapy in premenopausal and postmenopausal women with hormone receptor positive early breast cancer.
- In metastatic HER2 positive breast cancer there are now multiple lines of HER2 targeted therapies.

Sources and selection criteria

We used PubMed to identify recent published updates on the medical management of breast cancer. We also referenced presentations from international conferences and consulted with other experts in the breast cancer field.

Fig 1 Incidence of breast cancer in women and mortality rates in the United Kingdom over the past 30 years. Data from Cancer Research UK.

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Previous articles in this series

- Skin disease in pregnancy (BMJ 2014;348:g3489)
- Management of cutaneous viral warts (BMJ 2014;348:g3339)
- Posterior circulation ischaemic stroke (BMJ 2014;348:g3175)
- Managing common breastfeeding problems in the community (BMJ 2014;348:g2954)
- Spontaneous pneumothorax (BMJ 2014;348:g2928)
staging and local protocols. No significant difference was found in the risk of local or distant relapse at 6.3 years’ median follow-up between the SLNB only arm (about 27% of whom should have had further axillary disease) and the completion ALND arm. It was postulated that adjuvant therapy (especially breast radiotherapy, which reaches the lower axillae) eradicates residual axillary disease.

There is no international consensus as to which patients require ALND after a positive SLNB, and recent guidelines suggest that most women with one or two positive SLNBs who are having breast conservation surgery followed by breast radiotherapy may not need ALND. In addition, a recent trial that compared completion ALND with axillary radiotherapy for SLN positive axillae found that radiotherapy provided similar disease control to ALND, with less toxicity.

**Pathology and molecular subtyping: deciding on appropriate adjuvant therapy**

The planning of adjuvant postsurgical therapy in breast cancer is dictated by the pathology report, in which tumour burden is reported by tumour and axillary nodal status. Tumour biology is reported as histological grade, expression of the hormone receptors (oestrogen receptor and progesterone receptor), and amplification status of the HER2 gene. These factors are combined to estimate the prognosis and hence likely benefit from adjuvant therapies, often using online web based tools, such as Adjuvant Online! or the PREDICT tool, which incorporates the proliferation marker, Ki67, in its algorithm.

Additional molecular tests can be performed to give more information on tumour biology and improve the prediction of prognosis. These tests have been driven by the recognition of distinct molecular subtypes of breast cancer (fig 2). In particular, these tests can help differentiate between the two major groups of oestrogen receptor positive breast cancer—high proliferation cancers with a poor prognosis (luminal B tumours) and low proliferation cancers with a good prognosis (luminal A tumours).

The most widely used prognostic test is the Oncotype DX assay. This 21 gene assay on paraffin blocks is used to calculate a recurrence score and is currently validated in women with oestrogen receptor positive, lymph node negative cancers (fig 3). MammaPrint is another gene assay that uses 70 genes to estimate prognosis but is currently performed only on frozen material. In the UK, the National Institute for Health and Care Excellence recommends Oncotype DX to aid decisions about chemotherapy after surgery in some patients with oestrogen receptor positive, lymph node negative early breast cancer. Although these tests do not directly differentiate between luminal A and luminal B subtypes, they do assay the differences in biology that underlie these two subtypes.

**Adjuvant systemic therapy in early breast cancer**

Hormone treatment in the first five years

The aim of adjuvant therapy is to increase the chance of cure by eradicating micrometastatic disease. About 80% of breast cancers are oestrogen receptor positive. For these cancers, five years of adjuvant tamoxifen, a selective oestrogen receptor modulator, reduces the relative risk of relapse by 41% and death from breast cancer by 31%. Tamoxifen remains the standard of care for premenopausal women.

For postmenopausal women, aromatase inhibitors have been shown to be superior to tamoxifen. Two large trials (ATAC and BIG1-98) of nearly 10000 women compared five years of an aromatase inhibitor with five years of tamoxifen with a mean follow-up of 5.8 years. They showed a 2.9% absolute decrease in recurrence (9.6% vs 12.6%; P<0.001) favouring the aromatase inhibitor arm, although the absolute improvement in overall survival was small. Adverse effects that are more common with aromatase inhibitors than with tamoxifen include hot flushes, arthralgias, and bone thinning. For patients taking aromatase inhibitors, it
is important to monitor bone mineral density at baseline and every two years in the setting of osteopenia or osteoporosis, with calcium and vitamin D replacement considered in those with osteopenia, and the addition of a bisphosphonate or denosumab in those with osteoporosis. Women who are premenopausal at diagnosis but later become postmenopausal (naturally or as a result of chemotherapy), benefit from switching to an aromatase inhibitor after two to three years of tamoxifen.

**Adjuvant hormonal therapy extended beyond five years**

In oestrogen receptor positive breast cancer, as many recurrences occur after five years’ follow-up as in the first five years. For women who complete five years of tamoxifen and are postmenopausal, there is a 42% relative risk reduction (hazard ratio 0.57; P<0.001) with a further five years of the non-steroidal aromatase inhibitor letrozole.

For women who remain premenopausal after five years of tamoxifen, or who are intolerant of aromatase inhibitors, recent evidence suggests benefit of continuing tamoxifen beyond five years. The ATLAS trial of nearly 7000 women with oestrogen receptor positive early breast cancer reported a further reduction in recurrence (617 recurrences v 711; P=0.002) and breast cancer mortality (331 deaths v 397 deaths; P=0.01) for women who continue tamoxifen to 10 years, rather than stopping at five years. In a recent meta-analysis of five trials of extended adjuvant tamoxifen (>20000 women), the absolute risk reduction was 2.1% in lymph node negative (number needed to treat 49) and 4.1% in lymph node positive (25) patients. The risk of endometrial cancer was increased during years 5-14 in women who continued tamoxifen compared with those who stopped after five years (3.1% v 1.6%).

Similar results were seen in the ATTom trial of 6953 women. Pooled data from the ATLAS and ATTom trials confirm that, compared with no endocrine therapy, 10 years of adjuvant tamoxifen reduces death from breast cancer by one third in the first 10 years of follow-up, with a continued benefit beyond 10 years. Continued adjuvant endocrine therapy for 10 years has become a standard option, especially for women who originally had node positive breast cancer.

**Chemotherapy**

Combination adjuvant chemotherapy reduces the relative risk of death from breast cancer by about a third, with the absolute risk reduction depending on the risk of relapse. However, in many patients who receive adjuvant chemotherapy, the improvement in survival is small, because their chance of being cured by surgery and hormone therapy alone is high. Selection of which patients actually need chemotherapy is a major area of research. Molecular tests such as Oncotype DX improve the prediction of prognosis and can help identify which patients are likely to be cured by hormone therapy and surgery alone. However, many patients achieve an intermediate result with these molecular tests, and the management of these women is the subject of large trials that have completed accrual but are yet to report (TAILORx (NCT00310180) and MINDACT (NCT00633589)). Recent studies have also examined how morbidity from chemotherapy can be reduced by refining chemotherapy schedules, and such schedules are increasingly being used worldwide. As well as acute side effects, many chemotherapy schedules for breast cancer are associated with a low (<1%) risk of secondary myeloid cancers and cardiomyopathy.

**HER2 directed therapy**

About 15% of breast cancers have amplification of the HER2 gene, and these cancers have an intrinsically worse prognosis than other cancers. Trastuzumab is a monoclonal antibody against the extracellular domain of the HER2 receptor, and given every three weeks for a year improves disease-free survival (218 v 321 recurrence events favouring trastuzumab arm; hazard ratio 0.64; P<0.0001) and overall survival (59 v 90 deaths favouring trastuzumab arm; 0.66; P=0.0115). Trastuzumab has few adverse effects, although about 3% of patients experience a drop in left ventricular function, which is usually reversible. After treatment with trastuzumab is interrupted and an angiotensin converting enzyme inhibitor is started, many patients with left ventricular dysfunction can restart and complete the course of trastuzumab.

**Bisphosphonates**

A recent meta-analysis of 36 randomised controlled trials found that treatment with bisphosphonates is associated with a reduced risk of recurrence of breast cancer in postmenopausal women only. In the analysis of more than 11000 postmenopausal women, those treated with bisphosphonates had significantly fewer distant recurrences (18.4% v 21.9%; P<0.001) and fewer bone recurrences (5.9% v 8.8%; P<0.001) than those not taking bisphosphonates. Currently, this evidence has not translated into routine use of bisphosphonates solely for this purpose.

**Neoadjuvant therapy and locally advanced breast cancer**

Patients with large tumours currently not suitable for conservative surgery can be treated with preoperative
Chemotherapy, HER2 targeted therapy, or endocrine therapy to downstage the tumour and to facilitate breast conserving surgery. Neoadjuvant therapy in this setting also provides the opportunity to assess sensitivity to systemic therapy by monitoring response during neoadjuvant treatment before surgical excision. Patients who achieve a complete pathological response to chemotherapy, especially those with oestrogen receptor negative breast cancer, have a good prognosis. Patients with locally advanced breast cancer may start chemotherapy to reduce tumour bulk before mastectomy. Inflammatory breast cancer presents with erythema and oedema of the breast, with or without an underlying mass. This type of cancer is less likely to be oestrogen receptor positive and more likely to be HER2 positive than non-inflammatory breast cancers. Optimal treatment is usually preoperative chemotherapy, followed by surgery or radiotherapy (or both) using a multidisciplinary approach.

Management of advanced breast cancer

The aim of systemic therapy in advanced breast cancer is to palliate symptoms, control disease, and improve overall survival, while minimising the toxicity of treatment. Median survival after distant metastasis varies according to breast cancer subtype. In historical series, median duration of survival after distant metastasis varied from 2.2 years for luminal A subtype cancer to 0.5 years for basal-like breast cancers. Over the past three decades, overall survival has improved substantially, particularly in HER2 positive breast cancer. Metastatic breast cancer remains incurable in all but a few patients, yet many patients continue to live for many years with a good quality of life.

Hormone therapy

For oestrogen receptor positive metastatic disease, hormone treatment is recommended as firstline therapy, in the absence of life threatening visceral disease. The choice of hormone therapy depends on previous treatments and menopausal status. Resistance to hormone therapy in the metastatic setting is inevitable, and recent research has focused on attempts to restore sensitivity. The enzyme mTOR (mammalian target of rapamycin) is activated in many oestrogen receptor positive cancers that become resistant to hormone therapy. The combination of everolimus, an inhibitor of mTOR, with the hormone therapy exemestane controls disease for substantially longer than exemestane and placebo (median progression-free survival 10.6 v 4.1 months; P=0.001). Everolimus can have serious adverse effects, with stomatitis, rash, diarrhoea, fatigue, and pneumonitis being the most common. These adverse effects must be carefully monitored and treated promptly. Everolimus is licensed in Europe and North America for the treatment of advanced hormone receptor positive, HER2 negative breast cancer, although access to drugs varies. The inhibition of many other pathways similar to mTOR using targeted therapies is being investigated in phase I-III clinical trials.

Chemotherapy

Chemotherapy is used for hormone resistant cancer, hormone receptor negative disease, and rapidly progressive disease, as well as most HER2 positive cancers irrespective of oestrogen receptor status. The choice of which chemotherapy to use depends on patient factors (such as performance status, comorbidities), acceptance of potential toxicity such as alopecia, tumour factors (for example, triple negative v HER2 positive), and duration and response to previous chemotherapy. It is often given for a fixed number of cycles, especially with regimens that incur toxicity, although some regimens may be given long term (for example, paclitaxel and capecitabine). There is no consensus on the optimal duration of chemotherapy.

HER2 amplified breast cancer

In the past HER2 amplified breast cancer had a poor prognosis, but medical treatment has improved this (fig 4). The monoclonal antibody trastuzumab added to taxane chemotherapy significantly improves overall survival (25.1 v 20.3 months; P=0.046) in patients who have not received adjuvant trastuzumab. In patients who progress after trastuzumab, lapatinib—a small molecule kinase inhibitor of HER2—is approved in combination with capecitabine as second line treatment.

Further advances have been made recently through better targeting of HER2. In a phase III study, more than 800
patients were randomised to either docetaxel, trastuzumab, and pertuzumab or docetaxel, trastuzumab, and placebo. Combined inhibition of HER2 with pertuzumab, another monoclonal antibody that inhibits HER2 by blocking dimerisation with HER3, and trastuzumab, improved disease control by 6.1 months (18.5 v 12.4 months; P=0.001), 16 and overall survival (hazard ratio 0.66; P=0.001). 17 The addition of pertuzumab resulted in a modest increase in the side effects of diarrhoea and infections.

Trastuzumab-emtansine is an antibody-drug conjugate that specifically targets chemotherapy to HER2 positive breast cancer cells. 18 In the randomised phase III EMILIA study, this treatment was better tolerated than standard lapatinib and capecitabine chemotherapy and also improved disease control (9.6 v 6.4 months; P<0.001) and overall survival (30.9 v 25.1 months; P<0.001). 19 As a consequence of these steady improvements, the median survival of a woman with HER2 positive metastatic breast cancer diagnosed today is more than three years. 19

Preventing complications from skeletal metastases in breast cancer

Bone metastases occur in 60-80% of patients with advanced disease. 40 41 Skeletal related events include pain, fractures, and cord compression from extraosseous extension of vertebral metastases. These effects are reduced by the use of bisphosphonates, which inhibit osteoclast mediated bone resorption. 42

Denosumab is a subcutaneously injected monoclonal antibody that inhibits the membrane protein known as the RANK ligand, and this prevents the activation of osteoclast mediated bone destruction. 39 In a randomised study of denosumab versus zoledronic acid in more than 2000 patients with breast cancer and bone metastases, denosumab was more effective in reducing skeletal related events. 43 Bisphosphonates and denosumab, can cause hypocalcaemia, so calcium and vitamin D supplementation should be considered. The incidence of osteonecrosis of the jaw is around 0.5-1.0% a year in patients taking either of these agents, 45 and patients taking them should maintain good oral hygiene and avoid major invasive dental surgery.

Brain metastases from advanced breast cancer

As the treatment of advanced breast cancer improves, with better control of extracranial disease, the problem of cerebral metastases has become more evident, particularly in HER2 positive patients, because drugs such as trastuzumab cannot cross the blood-brain barrier. 46 Whole brain radiotherapy is the standard treatment for multiple brain metastases. Patients with solitary metastases, or oligometastatic disease, may be considered for surgical debulking, and stereotactic radiotherapy such as the CyberKnife and Gamma Knife systems. Some women with brain metastases have a relatively good prognosis with treatment, and can live for years after these metastases are diagnosed. 47

Where are we heading in the management of breast cancer?

The somatic genetic events that cause breast cancer have recently been described in detail, 48 49 and it is becoming evident that breast cancer is a highly heterogeneous disease at the genetic level. For cancers with HER2 amplification, there is substantial cause for optimism that, as new treatments for metastatic HER2 positive disease are brought into the adjuvant setting, we are on the way to curing most women with this form of breast cancer. This illustrates the benefit of identifying, and then targeting, the key genetic event that has driven the development of breast cancer.

Yet many other potentially targetable events occur in just a small proportion of breast cancers, and this presents a major challenge for academic oncology to develop strategies to target these rare genetic events. We are on the brink of an era of diverse molecular stratification of breast cancer, and the development of increasingly personalised medicine. Through such approaches, the survival rates of patients with breast cancer are likely to continue to steadily improve.

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