Adjuvant treatment for breast cancer

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Abstract

Adjuvant treatment for breast cancer is given following primary surgical management and aims to reduce the risk of recurrence (both local and distant) as well as improve survival rates. Radiotherapy is delivered to reduce local recurrence risk. Whole breast radiotherapy is considered standard treatment following breast-conserving surgery for invasive cancer and is also considered after mastectomy depending on pathological risk factors. Systemic therapies (such as chemotherapy, endocrine treatment and biological therapy) reduce the risk of distant metastases and improve overall survival. The decision to advise adjuvant treatment is complex (taking into account both prognostic and patient factors) and is made with the patient following a multidisciplinary team meeting. It is now common practice to employ benefit-risk calculators in the clinical setting to aid treatment decision making. Recent major advances in both systemic treatments and radiotherapy techniques have led to more personalized treatment for patients with the aim to reduce breast cancer mortality even further.

Keywords Aromatase inhibitors; chemotherapy; endocrine therapy; radiotherapy; tamoxifen

Introduction

Although the incidence of breast cancer continues to increase, survival rates have also improved as a result of earlier detection and improved treatment, of which adjuvant treatment is recognized as a key component.[1] Adjuvant treatment is given after surgery for breast cancer. It may be separated into local treatment (radiotherapy) and systemic treatments (chemotherapy, endocrine and biological therapies). The aim of adjuvant treatment is to reduce the risk of relapse (both local and distant) and to improve disease-free and overall survival.

The decisions regarding adjuvant treatment are made with the patient following multidisciplinary team meeting discussions. Factors taken into account include tumour size, histology, nodal status and expression of various receptors (oestrogen, progesterone and human epidermal growth factor receptor 2 (HER-2). Other factors that must be considered include past medical history, performance status, menopausal status and family history of breast/ovarian cancer.

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The decision to advise adjuvant treatment is not simple. A number of online benefit risk calculators have been developed to help determine appropriate candidates for adjuvant chemotherapy. These include Adjuvant! Online) http://www.adjuvantonline.com) and 'PREDICT' (http://www.predict.nhs.uk). Both of these programs use a risk-stratified approach, using the age, co-morbidities and tumour prognostic characteristics, to present the risks of recurrence and 10-year mortality figures, and to estimate the benefits of adjuvant endocrine treatment and chemotherapy.

Radiotherapy

The aim of adjuvant radiotherapy is to eradicate any local tumour deposits remaining following surgery, whether this may be a mastectomy or breast conserving surgery.

Adjuvant radiotherapy to the whole breast following a wide local excision reduces the risk of local recurrence by two-thirds. The benefit of whole breast radiotherapy is supported by the 2011 meta-analysis performed by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) which showed a significant reduction in local recurrence compared to surgery alone but only a small effect on mortality rates within the first five years after treatment.[2]

Whole breast radiotherapy is considered standard treatment after breast conservation surgery for invasive disease and also following surgery for high-grade ductal carcinoma in-situ (DCIS). Adjuvant radiotherapy is usually not given in cases of small volume low-grade DCIS as the risk of tumour recurrence is thought to be lower (Figure 1).

Conventionally in the UK, radiotherapy is delivered over 3 weeks, giving 40 Gy in 15 fractions. This regimen gained dominance after the results of the START trial suggested that this shorter fractionation schedule was safe and effective.[3]

Whole breast radiotherapy is associated with both acute and longer-term toxicities. Toxicities include fatigue, skin reactions, lymphoedema, breast skin fibrosis, and the more uncommon toxicities of pneumonitis, rib fracture, cardiotoxicity and angiosarcoma.

A radiotherapy boost to the tumour bed after whole breast radiotherapy is considered if there are high risk features for recurrence, such as young age, pathologically involved nodes or

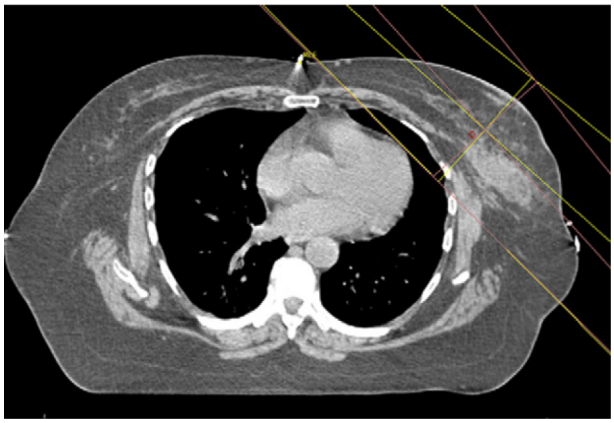

Figure 1 CT planning slice showing two tangential fields delivering radiotherapy to a left breast following wide local excision of an early breast cancer.

lymphovascular invasion. A boost is planned using localization clips inserted at surgery. The use of a boost can be associated with poorer cosmesis.

Multiple studies have shown that post-mastectomy radiotherapy leads to a decrease in the rate of locoregional recurrence (by two-thirds) and an increase in long-term survival. Chest wall radiotherapy is recommended for patients whose disease involves:

- Tumour size greater than 5 cm
- Four or more pathologically involved axillary lymph nodes
- Involved surgical margins or extensive lymphovascular invasion

Results from the SUPREMO trial, a phase 3 randomized study assessing the role of adjuvant chest wall radiotherapy in intermediate risk breast cancer, are awaited.

The risk for a locoregional recurrence increases with the number of positive nodes identified. If four or more axillary nodes contain metastatic tumour after axillary clearance, radiotherapy should be delivered to the supraclavicular nodes (SCF nodes). Radiotherapy to the SCF nodes should also be considered if there are poor prognostic features in women who have one to three nodes involved. Axillary radiotherapy after an axillary node clearance is not recommended due to the increased risk of lymphoedema. Radiotherapy to the axilla may be performed if axillary surgery does not occur because of patient wishes or anaesthetic risk. The AMAROS study indicated that both axillary clearance and axillary radiotherapy after a positive sentinel lymph node biopsy have excellent and comparable regional control of disease, and that radiotherapy to the axilla has a lower risk of short and long-term lymphoedema.[4]

Systemic adjuvant therapy

Systemic adjuvant therapy is used in the attempt to eradicate occult microscopic metastatic disease, thereby trying to prevent incurable distant relapse. The decision to use systemic treatment takes into account a number of prognostic factors, which include stage (tumour size and nodal status) and tumour biology. The

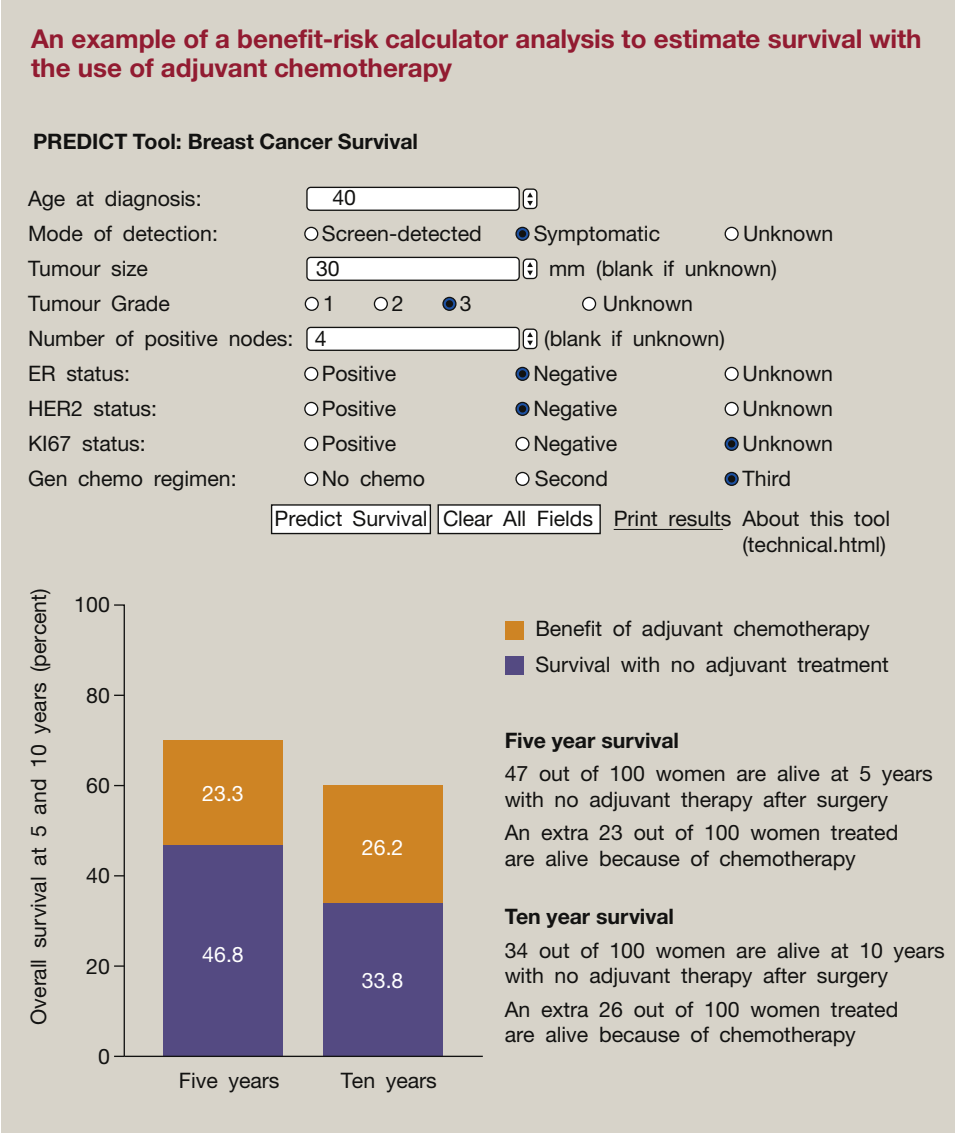

Figure 2

expression of ER and HER2 receptors is used to predict response to endocrine and anti-HER2 therapies. It is now common practice in the clinical environment to employ benefit-risk calculators (such as Adjuvant! Online and PREDICT, Figure 2) to estimate prognosis and determine patients who may benefit from treatment. These tools provide actuarial survival curves or pictorial outputs.

The development of genetic profiling using microarray technology is a relatively recent approach to select women who may benefit from adjuvant chemotherapy. EndoPredict (EPclin score), Oncotype DX Breast Recurrence Score and Prosigna are used routinely to guide adjuvant chemotherapy decisions for patients with ER positive, HER2 negative and lymph node negative (including micrometastastic disease) early breast cancer.

Chemotherapy

EBCTCG meta-analyses have shown that the use of adjuvant polychemotherapy is associated with a proportional reduction in recurrence of 23% and a reduction in breast cancer mortality of 17%. The absolute benefits do vary considerably across patient groups and are dependent on age and somewhat less dependent on which chemotherapy agent is used, the additional use of endocrine therapy and histopathological criteria.

There are a number of differing chemotherapy regimens and protocols available. Since the initial trials by Bonadonna and colleagues in the 1970s, these have moved from the use of CMF (cyclophosphamide, methotrexate and fluorouracil) to anthracycline-based combinations (e.g. FEC, which uses fluorouracil, epirubicin and cyclophosphamide).[5] Compared to the CMF regimen, anthracycline-based regimens lead to a greater reduction in both recurrence and breast cancer mortality rates. Adjuvant regimens are usually given on a 3-weekly basis for six cycles in total.

NICE has now authorized the use of docetaxel in chemotherapy regimens for node-positive patients (higher risk of recurrence and metastatic disease).[6] Taxane-based regimens (such as those using docetaxel) do come at a cost of higher toxicity, so patients considered for this treatment should have minimal comorbidities and good performance status. The most common taxane-based regimen used is FEC-T (three cycles of FEC followed by three cycles of docetaxel).

Chemotherapy has a number of short-term side-effects including fatigue, mucositis, nausea/vomiting, hair loss and myelosuppression. Longer term toxicities include early menopause secondary to ovarian failure. There is a small risk of leukaemia with alkylating agents and long term cardiotoxicity with anthracyclines.

Despite the abundance of randomized evidence and the number of international treatment guidelines available, the use of chemotherapy remains an intensively debated and often controversial area.

Endocrine therapy

Approximately 60–80% of breast cancers are oestrogen-dependent. Toxicity with endocrine therapy is less than for chemotherapy. The interruption of the ER signaling pathway has been shown to reduce the risk of recurrence. Endocrine therapy achieves its aim by either reducing the production of oestrogen (via ovarian suppression/ablation or aromatase inhibitor use) or interfering with the oestrogen – oestrogen receptor complex configuration (mechanism of tamoxifen).

Adjuvant endocrine therapy is considered for all women who have ER-positive breast cancer. There is no benefit in ER-negative breast cancer.

Pre-menopausal patients

Tamoxifen is a selective oestrogen receptor modulator (SERM) that inhibits the growth of breast cancer cells by competitive antagonism of the oestrogen receptor by binding to one of the two activating regions of the receptor. It acts by inhibiting the translocation and nuclear binding of the oestrogen receptor. Tamoxifen, which is administered as a 20-mg tablet on a once-daily basis, has oestrogenic agonist, partial agonistic and antagonistic effects depending on the target tissue. This accounts for some of its beneficial effects and risks. Agonistic effects include an increased incidence of endometrial thickening and cancer, preservation of bone mineral density in postmenopausal women and a reduction in cholesterol levels. The most common toxicities of tamoxifen include hot flushes, vaginal discharge and increased risk of thromboembolic disease (i.e. deep vein thrombosis and pulmonary embolism).

Data from the 2011 EBCTCG meta-analysis showed that five years of adjuvant tamoxifen led to a significant reduction in the annual recurrence rate, decreased the risk of breast cancer related mortality and contralateral breast cancer rates.[7] The current practice is to offer tamoxifen for a 5-year duration. Both the ATLAS and the aTTOM trials, however, which randomly assigned women to five or longer durations of tamoxifen treatment, showed that longer durations of treatment led to greater reductions in recurrence rates and mortality figures.[8] Based on these data, the risk and benefits of extended duration of tamoxifen therapy for a 10-year duration is considered in all patients with ER positive invasive breast cancer.

Ovarian function suppression (OFS) can also be considered for premenopausal women. This can be achieved by pelvic radiation, oophorectomy or medically with goserelin. The benefits of OFS were reported in the 2005 EBCTCG meta-analysis which showed a significant reduction in the risk of recurrence compared with observation and a significant reduction in breast cancer deaths (studied women under 50 years of age).

Postmenopausal patients

All postmenopausal women who are candidates for endocrine therapy should be offered treatment, regardless of age. This can be using tamoxifen or aromatase inhibitors, or a sequential combination of both.

Aromatase inhibitors (AIs) block the peripheral conversion of androgens to oestogens. This mechanism of action is therefore used to its full advantage in postmenopausal women in whom the production of oestrogen is by peripheral aromatisation, mainly in subcutaneous fat.

Anastrozole, letrozole and exemestane (all third-generation AIs) are commonly used. The efficacy among these is generally considered comparable despite their different actions of mechanism. These AIs are used in both early and advanced breast cancer. Five years of AI therapy has been shown to improve recurrence and survival outcomes compared with tamoxifen.

Women who have low-risk breast cancer and are intolerant of tamoxifen as well as postmenopausal women with intermediate and high risk of recurrent disease should be offered AI therapy.[9] Patients who are intolerant of tamoxifen, such as those at significant risk or history of thromboembolic disease, should be considered for AIs.

A five-year course of sequential endocrine therapy (tamoxifen for two or three years followed by an AI to five years) leads to a significant reduction in breast cancer recurrence and reduction in breast cancer mortality.[10,11]

The Canadian MA17 trial showed an improvement in disease-free survival in postmenopausal women who received 5 years of letrozole (compared to placebo) after completing a 5-year course of tamoxifen.[12] There was a small benefit in overall survival for patients with node-positive disease. EBCTCG meta-analysis showed that extended endocrine therapy with AI led to a 24% reduction in the risk of any recurrence; a 15% reduction in the risk of distant recurrence, and a non-significant reduction in breast cancer mortality.[13] Extended duration therapy of more than 5 years is offered to postmenopausal patients who are at medium or high risk of disease recurrence and who have been taking tamoxifen for 2–5 years.

AIs are associated with musculoskeletal discomfort, hypercholesterolaemia and increased cardiovascular risk. There is a higher risk of osteoporosis and associated fractures, so all patients should have a bone density scan at the time of commencing treatment and receive advice and treatment as necessary if found to have osteopenia or osteoporosis.

Adjuvant trastuzumab (Herceptin)

Around 15% of patients with early breast cancer have HER-2 positive disease and testing for HER-2 is now routine in breast pathology laboratories by immunohistochemical or molecular techniques. Amplification of the HER-2 gene is associated with a poorer prognosis and higher risk of relapse. Trastuzumab is a humanized monoclonal antibody developed against the HER-2 transmembrane epidermal growth factor receptor. Four large RCTs showed trastuzumab was associated with a 45% reduction in recurrence risk. Standard adjuvant trastuzumab is given three weekly for 12 months.

Trastuzumab is generally very well tolerated but there is the small risk of cardiac dysfunction and reversible cardiomyopathy. Trastuzumab does not cause myocyte loss in contrast to anthracycline chemotherapy. Cardiac function (i.e. left ventricular ejection fraction) should be assessed prior to chemotherapy and after its completed course before commencing trastuzumab (and during treatment). The left ventricular ejection fraction can be measured using echocardiogram or radionuclide MUGA scan, but the same monitoring modality should be used throughout the course of treatment.[14] Other cardiac risk factors such as hypertension should be controlled and lifestyle modifications (e.g. smoking cessation) made as appropriate.

Other HER-2 targeting drugs e.g. pertuzumab are currently not recommended for adjuvant treatment in the UK. .

Male breast cancer

This is relatively uncommon, accounting for less than 1% of cases and usually occurs 10 years later in age compared to women. Treatment follows the same principles as in females, with tamoxifen used as the first-line endocrine management.

Conclusion

Adjuvant treatment has played a key role in reducing the risk of breast cancer recurrence and in improving survival. It is hoped that further advances in therapy (in both systemic management and radiotherapy) will help in the personalisation of care and lead to even more successful treatments. ◆

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