ABC of breast diseases

Medical treatment of early breast cancer. I: adjuvant treatment

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The past decade has seen an impressive fall of around 15% in deaths from breast cancer in the United Kingdom, and this has occurred in the face of a rising incidence. This fall coincides with the widespread national uptake of adjuvant systemic therapy and with increasing evidence of its benefit for survival.

More than half the women with operable breast cancer who receive only locoregional treatment die from metastatic disease. This indicates that micrometastases are present at initial clinical presentation. The major risk factors for the development of metastatic disease are the involvement of axillary nodes, a poor histological grade, large tumour size, and histological evidence of lymphovascular invasion around the tumour site. The absence of oestrogen and progesterone receptors, and the overexpression of the human epidermal growth factor receptor 2 (HER2), also carry an adverse prognosis. The way to improve survival is to give these women systemic medical treatment, including endocrine therapy, chemotherapy, or targeted therapy with trastuzumab along with surgery.

Systemic treatment may be given after (adjuvant) or before (neoadjuvant, primary, or preoperative) locoregional treatment. Adjuvant treatment has been shown to be effective in randomised clinical trials, whereas the evaluation of neoadjuvant systemic therapy is ongoing. The effectiveness of adjuvant treatment cannot be assessed in individual patients because there is no overt disease to monitor, and trials that compare different adjuvant therapies take years to produce results; this is an important problem when trying to assess the role of active new drugs in adjuvant therapy. In contrast, the immediate effect of neoadjuvant treatment can be assessed by monitoring the response of the primary tumour to treatment. Regressions in large tumours may allow breast conserving surgery rather than mastectomy.

Treatments

Polychemotherapy, oophorectomy (including the use of gonadotrophin releasing hormone analogues), tamoxifen, and aromatase inhibitors in postmenopausal women all reduce the annual rates of tumour recurrence and death. These treatments improve long term survival substantially. Adjuvant endocrine treatments are effective only in patients with oestrogen receptor positive cancer or progesterone receptor positive cancer.

Tamoxifen

- Is a partial oestrogen agonist (has antagonistic actions in breast cancers, but has agonist actions on endometrium, lipids, and bone)
- Is as effective at 20 mg/day as at higher doses
- Is effective in all age groups, and in premenopausal and postmenopausal women
- Is more effective when given for five years rather than two, but no evidence shows that tamoxifen is of additional benefit if taken for more than five years, and it may be detrimental
- Reduces risk of contralateral breast cancer by 40-50%
- May be less effective against HER2 positive tumours
- Is more effective when given after chemotherapy (when this is also indicated) rather than concurrently.

This article is adapted from the 3rd edition of the **ABC of Breast Diseases** (Blackwell Publishing), available from all good medical bookshops, including www.hammicksbma.com

Trends since 1950 in age standardised death rates for breast cancer and other types of cancer among women in the United Kingdom. The fall in mortality since 1990 has been caused mainly by the introduction of adjuvant therapy as a consequence of results from clinical trials. Data from WHO mortality and United Nations population estimates

Risk categories for early breast cancer

Category

Low risk	Node negative and all of the below: Tumour size ≤ 2 cm Grade I No peritumoural vascular invasion HER2 negative Age ≥ 35 years
Intermediate risk	Node negative and at least one of the below: Tumour size > 2 cm Grade II-III Peritumoural vascular invasion HER2 positive Age < 35 years; or Node positive (1-3 nodes) and HER2 negative
High risk	Node positive (1-3 nodes) and HER2 positive; or Node positive (≥ 4 nodes)

Adapted from *Ann Oncol* 2005;16:1669-83

Outline of options for systemic treatment of large, operable breast cancer

Aromatase inhibitors

- In contrast to tamoxifen, act by inhibiting oestrogen synthesis
- Include the non-steroidal agents anastrozole and letrozole, and the steroidal agent exemestane
- Are effective only in postmenopausal women
- Improve disease free and metastatic free survival better than tamoxifen
- Improve disease-free survival if patients are switched after two or three years of tamoxifen rather than continuing on tamoxifen
- Reduce the risk of recurrence when used as extended adjuvant therapy after five years of tamoxifen
- Improve survival in node positive patients
- Reduce the risk of contralateral breast cancer by a further 40-50% when given instead of, or after, tamoxifen
- May be more effective than tamoxifen against HER2 positive tumours.

Oophorectomy (including gonadotrophin releasing hormone analogues)

- Is of benefit only in premenopausal women
- May be as effective as older cyclophosphamide, methotrexate, and fluorouracil chemotherapy (CMF) schedules against oestrogen receptor positive tumours, but has not been assessed against more effective modern chemotherapy
- May provide further benefit after chemotherapy in premenopausal women who continue to menstruate.

Chemotherapy

Clinical trials have shown that:

- The benefits of chemotherapy are greatest in younger women but are still important up to 70 years
- The absolute benefit increases with increasing adverse prognostic factors, which include: number of involved nodes, if the tumour is oestrogen receptor negative, if the tumour has a poor histological grade, and with lymphovascular invasion, increasing size of tumour, or young age (especially ≤ 35 years), and if the tumour is HER2 positive. These factors determine if chemotherapy should be used
- Chemotherapy does not seem to produce substantial benefits in postmenopausal women with grade I or II breast cancer that is oestrogen receptor rich and HER2 negative, and who receive appropriate endocrine treatment

Absolute risk reductions for recurrence and survival during the first 10 years after treatment, subdivided by duration of tamoxifen and by nodal status (after exclusion of women with oestrogen receptor poor disease). Adapted from *Lancet* 1998;351:1451-67

Adjuvant tamoxifen for five years reduces the annual breast cancer death rate by 31% (SE 3%) irrespective of the use of chemotherapy and of age. For oestrogen receptor positive tumours, the annual breast cancer mortality is similar during 0-4 years and 5-15 years. Five years of tamoxifen produces the same proportional reductions over 15 years, so that cumulative reduction in mortality is more than twice as large at 15 years as it is at five years

Estimated effects of 6 months of anthracycline based chemotherapy or 5 years of tamoxifen, or both, on breast cancer mortality

Systemic adjuvant treatment and age at diagnosis (years)	Effect on annual breast cancer mortality		15 year risk of death from breast cancer and absolute gain with treatment					
	Rate ratio	Proportional reduction (%)	Low risk patients		Moderate risk patients		High risk patients	
			Risk	Gain	Risk	Gain	Risk	Gain
<i>Chemotherapy only in oestrogen receptor poor or oestrogen receptor positive disease</i>								
None (any age)	1.0		12.5%		25.0%		50.0%	
Anthracycline (age <50)	0.62	38%	7.9%	4.6	16.3%	8.7	34.9%	15.1
Anthracycline (age 50-69)	0.80	20%	10.1%	2.4	20.6%	4.4	42.6%	7.4
<i>Endocrine or chemoendocrine therapy in oestrogen receptor positive disease</i>								
None (any age)	1.0		12.5%		25.0%		50.0%	
Tamoxifen (any age)	0.69	31%	8.8%	3.7	18.0%	7.0	38.0%	12.0
Anthracycline + tamoxifen (age <50)	0.62×0.69	57%	5.6%	6.9	11.6%	13.4	25.7%	24.3
Anthracycline + tamoxifen (age 50-69)	0.80×0.69	45%	7.1%	5.4	14.7%	10.3	31.8%	18.2

Modified from *Lancet* 2005;365:1687-717.

- Anthracycline-containing combinations using doxorubicin or epirubicin are more effective than traditional CMF chemotherapy combinations. Evidence indicates that adding taxanes (and particularly taxotere) to anthracyclines further improves survival in women with node positive disease
- Accelerated (sometimes called dose dense) chemotherapy given every two weeks with haemopoietic support from granulocyte colony stimulating factor may improve survival further in node positive disease
- Five year survival in women with node positive cancer has risen from around 65% without treatment, and from around 70% with CMF to around 85% with modern anthracycline-taxane combinations.

Trastuzumab

- Reduces the risk of early recurrence by about 50% when given with or after chemotherapy for a year
- Increased risk of cardiotoxicity (mainly congestive heart failure) when given with chemotherapy, especially with anthracycline
- Slight risk of cardiotoxicity when given after anthracycline, but higher when given concurrently.

Side effects of endocrine therapy

The side effects of endocrine treatment are greatest in premenopausal women. Tamoxifen may cause vaginal dryness or discharge, loss of libido, and hot flushes, and these may have considerable impact upon quality of life (although less than 5% of patients stop treatment because of side effects).

First line treatment for vaginal dryness is with a non-hormonal cream (such as Replens), but if this is not effective, locally applied oestrogen should be tried. Aromatase inhibitors also cause vaginal dryness; because even a fixed dose vaginal tablet, such as Vagifem, can produce systemic oestrogen spillover, caution is required when using them.

Clonidine is rarely effective at relieving flushing and so is not often used. In controlled trials, evening primrose oil has not produced substantial benefit. Megestrol acetate in a dose of 20 mg twice a day significantly improves flushing in 80% of patients; hot flushes often increase immediately after starting treatment and patients should be informed that treatment for two to four weeks is required to reduce the frequency of hot flushes. Venlafaxine and other serotonin reuptake inhibitors are partially effective for hot flushes, but can cause a dry mouth. A recent trial has shown that hormone replacement therapy increases the risk of recurrence, and so is not recommended. Tibolone is preferable to hormone replacement therapy and is effective at controlling symptoms induced by tamoxifen. An ongoing trial investigating tibolone's long term safety has not yet shown any increase in recurrence of breast cancer.

Prolonged use of tamoxifen is associated with a three to four times increased incidence of endometrial cancer and an increased risk of venous thromboembolism in postmenopausal women (although the absolute incidence of these serious side effects remains low). In contrast, tamoxifen decreases the risk of bone loss and osteoporosis, at least in postmenopausal women.

In postmenopausal women, new aromatase inhibitors (anastrozole, letrozole, and exemestane) cause fewer hot flushes, and less vaginal discharge, vaginal bleeding, endometrial cancer, and venous thromboembolism than tamoxifen. These drugs are, however, associated with an increased risk of fractures and osteoporosis. The main short term problems of aromatase inhibitors are joint and muscle pains; these occur in few women, but the pain can be severe and treatment may need to be stopped. The long term risks of these drugs on bone

Effect of age and characteristics of tumours on chemotherapy benefit

Characteristics	Gain in 10 year absolute survival gain with optimal chemotherapy
60 years, 2 cm, grade II, oestrogen receptor positive cancer, 1-3 nodes involved	4% (in addition to tamoxifen)
45 years, 3 cm, grade III, oestrogen receptor negative cancer, 4-9 nodes involved	27.5%

Data from www.Adjuvant!online

Side effects of drugs used for adjuvant treatment

Tamoxifen

- Venous thromboembolism
- Hot flushes
- Altered libido
- Gastrointestinal upset
- Vaginal discharge or dryness
- Menstrual disturbance
- Endometrial cancer (investigate any reported vaginal bleeding)
- Weight gain

Aromatase inhibitors

- Hot flushes (less than tamoxifen)
- Joint and muscle pains
- Osteoporosis
- Fatigue
- Vaginal dryness

Oophorectomy

- Induction of menopause
- Vaginal dryness
- Hot flushes
- Osteoporosis

Gonadotrophin releasing hormone analogues

- As for oophorectomy
- Pain and bruising at site of injection

Chemotherapy

- Fatigue and lethargy
- Alopecia (temporary)
- Nausea and vomiting
- Induction of menopause
- Risk of infection
- Oral mucositis
- Diarrhoea
- Weight gain
- Specific side effects of certain drugs

Trastuzumab

- Hypersensitivity
- Cardiotoxicity (mainly congestive heart failure)

Weight gain is often reported by women treated with tamoxifen or chemotherapy. Randomised trials have not found more weight gain in patients treated with tamoxifen than those who received placebo

Oophorectomy causes immediate (and often severe) menopausal symptoms, carries an increased risk of osteoporosis, and is inevitably associated with sterility

turnover, lipid metabolism, cardiovascular function, and cognitive function have yet to be determined.

Side effects of chemotherapy

Although hair loss is the most common concern of patients before starting chemotherapy, 80% report fatigue and lethargy as the most troublesome side effect. The alopecia caused by some chemotherapy regimens may be reduced by cooling the scalp. Nausea and vomiting are unpleasant side effects, but they can be controlled in most patients by appropriate antiemetic drugs including the serotonin-3 antagonists, granisetron and ondansetron. These should be used as first line treatment, even for moderately emetogenic chemotherapy.

Haematological toxicity (particularly neutropaenia) is a common side effect of most chemotherapy regimens, but neutropaenic infection occurs in about 10% of patients depending on the regimen. The lower the neutrophil nadir and the longer its duration, the greater the chance of sepsis developing. This requires urgent treatment with appropriate intravenous antibiotics and fluids. Trials have shown that dose reductions or delays in treatment may compromise efficacy, and for this reason haemopoietic support with granulocyte colony stimulating factor should be used in patients in whom neutropenia would otherwise compromise treatment. Ovarian suppression induced by chemotherapy with loss of fertility is an important problem for younger women; the risk of this increases rapidly at age 35. Gonadotrophin releasing hormone agonists may protect the ovaries against infertility or menopause induced by chemotherapy.

Other side effects of chemotherapy include oral mucositis. Some drugs have specific problems (for example, fluid retention with taxotere and neuropathy with either taxotere or taxol), and all chemotherapy requires specialist supervision.

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The ABC of Breast Diseases is edited by J Michael Dixon, consultant surgeon and senior lecturer in surgery, Edinburgh Breast Unit, Western General Hospital, Edinburgh.

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Antiemetic regimens during chemotherapy

Standard antiemetic schedules

- Intravenous dexamethasone (4-8 mg) and intravenous granisetron (3 mg) or ondansetron (8 mg) before chemotherapy, and oral dexamethasone 4 mg two to three times daily to take home for three days

Additional treatment when needed

- Oral granisetron (1 mg/day) or oral ondansetron (4 mg twice daily) for three to five days after chemotherapy
- Domperidone 20 mg four times daily
- Cyclizine 50 mg three times daily (or by infusional pump)
- Stemetil 5 mg four times daily (or by suppository)
- Lorazepam 1 mg twice daily (useful for anticipatory symptoms)

Further reading

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A case of "proper" flu

A few months ago I developed some non-specific symptoms—fatigue, malaise, and fever. I told myself that it was "just a virus," but as the weeks went by I began to worry. I scanned myself for other symptoms and identified nausea after meals, aversion to alcohol, and some vague gastrointestinal symptoms. "Perhaps it is something serious," I thought, "hepatitis, or even cancer." I had been on holiday to Venezuela earlier in the year, and so I began looking up tropical infections in textbooks.

Eventually I went to see my general practitioner and gave a rather confused account of my symptoms and concerns. I felt like a medical student making a bad job of a case presentation. Wisely he agreed to an impressive range of screening blood tests. The following week I received the results by email, as arranged: all normal except for viral serology suggesting a recent infection with influenza A.

I learnt a lot from this experience: the challenge of organising one's own symptoms into a coherent structure, the reality of patients' concerns about unlikely illnesses, the value to the patient of making a diagnosis even when there are no implications for management. Most of all, I can now empathise more with the paradoxical disappointment and frustration that some patients have when investigations are unrewarding (as they might well have been for me).

Feeling suitably embarrassed at my overactive imagination, I emailed my GP: "So it was just flu after all."

"Yes," he replied, "but at least it was 'proper' flu."

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