

BREAST CANCER

— treatment of early disease

By A. STANLEY, MRPHARMS

The incidence of breast cancer has been increasing in recent years, but modern treatment of the disease has meant that mortality has dropped.

This article outlines how chemotherapy, hormonal therapy, radiotherapy and surgery combine to treat early breast cancer

A woman about to receive radiotherapy for breast cancer

Breast cancer is a highly complex disease with many treatment options, including pharmacological therapy (chemotherapy, hormonal therapy and other drug therapy), radiotherapy and surgery. In many patients, it is a combination of these treatments that is thought to produce the best clinical outcome. This article will cover the areas of neoadjuvant (given before surgery to shrink the tumour) and adjuvant (given after surgery to eradicate micro-metastases) treatment for early breast cancer (see previous article, p409).

Radiotherapy High-energy radiation is used to eradicate breast cancer cells from a localised field of treatment. Radiotherapy may be indicated as adjuvant treatment following surgery to eradicate micro-metastatic disease from the breast or from the chest wall and loco-regional lymph nodes in high risk disease.

Chemotherapy Many cytotoxic drugs are active in breast cancer, and are currently used both before and after breast cancer surgery.

Dr Stanley is principal oncology pharmacist, Sandwell and West Birmingham Hospitals NHS Trust, and pharmacist, pan-Birmingham cancer network

Endocrine therapy Oestrogen is the main hormone involved in the development and growth of breast tumours. The aim of endocrine therapy is to deprive tumour cells of the proliferative stimulus of oestrogen. This can be achieved by blocking the oestrogen receptor on tumour cells (eg, tamoxifen) or by reducing the circulating levels of oestrogenic compounds (eg, ovarian ablation in pre-menopausal women or aromatase inhibitors in post-menopausal women). Endocrine therapy is active for breast tumours that express the oestrogen receptor (ER) or, to a lesser extent, the progesterone receptor (PgR). Endocrine therapy is currently used before and after surgery.

Biological therapy An expanding array of agents is being used, designed specifically to target particular cellular functions important to the cancer cell for survival or proliferation. The best characterised in breast cancer is trastuzumab (Herceptin), a monoclonal antibody targeting the ErbB2 (also known as Her-2) receptor. This cell surface receptor is over-expressed in a proportion (possibly a quarter) of breast cancers and the efficacy of trastuzumab is limited to patients with such breast cancers. Trastuzumab is currently used in the palliative treatment of metastatic breast cancer and is being evaluated as an adjuvant treatment in ongoing clinical trials.

Prevention Some women who do not have breast cancer can be identified as being at high risk of developing the disease (eg, first degree relatives have breast cancer). A double-blind, placebo-controlled, randomised trial of tamoxifen 20mg daily in 7,152 patients at high risk of developing breast cancer has been undertaken. The International Breast cancer Intervention Study (IBIS) showed that prophylactic tamoxifen reduces the risk of breast cancer by about a third, but the overall risk to benefit ratio for this use of tamoxifen is still unclear, due to the adverse effects of the drug in otherwise healthy women.¹

NEOADJUVANT TREATMENT

Neoadjuvant therapy includes the use of chemotherapy or hormonal therapy to shrink large tumours to facilitate more effective surgery. Neoadjuvant treatment is considered particularly useful in patients with smaller breasts, especially if those breasts contain large tumours.

Chemotherapy Doxorubicin and cyclophosphamide have been widely used in combination as neoadjuvant treatment. However, a recent trial concluded that the novel combination of vinorelbine and epirubicin is at least as effective as the established regimen, with less severe nausea, vomiting and alopecia.²

Hormonal therapy The use of tamoxifen as a neoadjuvant therapy for up to six months before surgery is well established. However, a recent study suggested that the aromatase inhibitor letrozole may be more effective. This study was a randomised, double-blind, double-dummy, multi-centre trial of neoadjuvant letrozole 2.5mg daily versus tamoxifen 20mg daily in post-menopausal women with ER or PgR positive breast cancer who were ineligible for breast-conserving surgery. Study medication was taken for four months before surgery unless the patients were withdrawn earlier due to progressive disease, an adverse event, or patient or investigator request. Patients receiving letrozole were more likely to receive breast-conserving surgery to remove their tumour than to lose the entire breast with a mastectomy. Baseline characteristics of both groups were well matched. Results are presented in Table 1.³

— SURGERY

Surgery for breast cancer is divided into that which aims to obliterate the breast (mastectomy) or conserve the breast (lumpectomy). These procedures are further sub-divided as follows:

- Simple mastectomy, where the entire breast tissue, including the axillary tail

(the line of lymph nodes under the arm) is removed together with the skin, nipple and areola. Samples are also taken from the lowest axillary lymph nodes to establish if the cancer has spread.

- Modified mastectomy where the same structures are removed as for simple mastectomy, together with the pectoralis minor muscle. This should lead to easier removal of the axillary lymph nodes.
- Wide local excision (a lumpectomy), where the breast lump is removed with at least a 1cm margin of normal tissue. Lymph node sampling also occurs.
- Quadrantectomy (a lumpectomy), where surgical removal of a greater volume of tissue than for wide local excision is involved, often because the tumour has a more diffuse appearance. As the name suggests, the whole of the quadrant that contains the tumour is excised and lymph node sampling occurs.

The choice of surgical operation is made after a discussion between the patient and the surgeon. The size of the tumour relative to the size of the breast, the desired cosmetic outcome and the patient's willingness to undergo further adjuvant treatment may all be factors that direct the discussion.

After surgery, it is vital to gather some histological data about the individual patient's breast cancer. This includes the status of a number of cell surface markers because this will dictate the treatment decisions from then on. These cell markers are oestrogen, progesterone and Her-2.

The question that inevitably follows curative surgery, whether it is mastectomy or lumpectomy, is that of adjuvant therapy. The question should not be as to its use — overwhelmingly now the role of adjuvant treatment has been shown to offer benefits — but whether it should be hormonal therapy, radiotherapy or chemotherapy, or a combination of these treatments.

— ADJUVANT RADIOTHERAPY

The first randomised trial of post-mastectomy irradiation in operable breast cancer was carried out at the Christie Hospital, Manchester, in 1948.⁴ Despite what would now be viewed as inadequate irradiation and variations in the delivery technique, this trial showed a 13 per cent reduction in local recurrence, although there was no effect on overall survival. Throughout the 1960s and 1970s, further studies showed that radiotherapy prevented local disease but not death from breast cancer. It was not until 1986 when the Stockholm Trial was completed

Table 1: Letrozole versus tamoxifen as neoadjuvant endocrine therapy

	Letrozole (n=154)	Tamoxifen (n=170)	P
Primary endpoint			
Overall response rate (complete response or partial response) determined by clinical palpation	55%	36%	<0.001
Secondary endpoints			
Response rate (complete response or partial response) determined by ultrasound	35%	25%	0.042
Response rate (complete response or partial response) determined by mammogram	34%	16%	<0.001
Percentage of patients eligible for breast conserving surgery	45%	35%	0.022

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that benefits were seen in terms of survival with the use of both pre- and post-operative radiotherapy.⁵ This result showed not only an improvement in terms of local control but also in terms of a decreased risk of distant metastases and better overall survival. However, even this study was dogged by changes in radiotherapy technique and variations in the overall dose received.

It is indeed these technical factors and the lack of homogeneity in the populations post-surgery that have plagued some of the overviews of radiotherapy studies. The overview has the advantage that, by reviewing data for large numbers of patients, it has the potential to detect small or moderate changes, which may not be evident in the individual studies. The first overview by Jack Cuzick, London in 1987 showed an excess in mortality in the irradiated group.^{6,7} This result was probably due to the variations in techniques and study populations. Several other overviews were attempted, with some of the studies with variations excluded from the analysis. Although this still often left several thousands of patients in the study, it did limit the power to detect effects, although the authors were able to refute the excess mortality claims originally identified by Professor Cuzick. However, it was not until 1995, when the Early Breast Cancer Trialists' Collaborative Group published its meta analysis (the Oxford Overview) of 17,273 breast cancer patients, that a consensus was reached.⁸

Despite showing a significant reduction in breast cancer incidence with radiotherapy, mortality was nullified by an equal and opposite increase in death from other causes (eg, heart failure, possibly precipitated or aggravated by left side chest irradiation). This left researchers with the overall conclusion that there was no net gain in survival. This position was supported by the Oxford Overview update in 2000.⁹

However, this is far from the end of the story and three recent studies which exam-

ine the combination of radiotherapy and chemotherapy or tamoxifen show positive results with long-term follow-up.¹⁰⁻¹² These studies are summarized in Table 2.

On the basis of the two studies in premenopausal patients,^{10,11} a consensus statement recommended that all premenopausal women with tumours larger than 5cm and where four or more axillary nodes are affected should receive post-operative radiotherapy and chemotherapy.¹³ The benefits are not clear in the lower risk patients, ie, those with one to three nodes involved.

As shall be seen later, chemotherapy for adjuvant early breast cancer is changing with the addition of anthracyclines (eg, doxorubicin, epirubicin) and the licensing of taxanes (eg, docetaxel, paclitaxel) for this group of patients. The increased efficacy of these treatments may remove the need for these patients to receive radiation. It should further be noted that radiotherapy techniques and quality assurance processes have also made considerable progress. The use of computed tomography planning, multi-field therapy and better beam position with multi-leaf collimators (which adjusts the size and shape of the beam) have led to a reduction in cardiac toxicity and morbidity.

ADJUVANT HORMONAL THERAPY

Breast cancer can potentially be treated by the manipulation of hormones. The mainstay of hormonal treatment is tamoxifen, a drug launched in 1974. Since then, numerous studies have shown that this oestrogen antagonist, which works predominantly at peripheral oestrogen receptors in the breast tissue, has a valuable role in the management of this disease. However, the final confirmation of its importance probably did not come until the Oxford Overview in 1998.¹⁴ This group reviewed individual patient data comparing tamoxifen with non-tamoxifen therapy in 37,000

women in 55 trials, all of which started before 1990. A group of approximately 8,000 women were excluded from the analysis because their tumour oestrogen receptor status was poor or negative and they were therefore not likely to benefit from tamoxifen. The overview was left with approximately 18,000 ER-positive women and 12,000 women whose ER status was not known, but of which about two-thirds were likely to be ER-positive.

The clear conclusion of this overview was that tamoxifen worked and seemed to bring benefit to all groups of women both in terms of recurrence reduction and lower mortality. Increased duration of exposure, up to five years, to tamoxifen seemed to increase the degree of the benefit (Table 3, p418).

Furthermore, the effect of tamoxifen was not dependant on nodal status, but there was a trend for better results in node positive patients (although the difference in the results was not statistically significant). In terms of age, women starting treatment under the age of 50 and over the age of 60 had a proportional reduction in mortality of 32 per cent and 34 per cent, respectively. The reduction in recurrence was 45 and 54 per cent, respectively. The overview concluded that there was a benefit to five years' treatment with tamoxifen in all women with ER-positive or ER-unknown tumours. It was also concluded that women with ER-negative and PgR-positive tumours had benefits in the same order as those for ER-positive patients if given five years of tamoxifen.

Five years of tamoxifen has also been shown to reduce the occurrence of contralateral breast cancer (a tumour in a patient already treated for cancer in the opposite breast). The Oxford Overview showed a 47 per cent reduction in incidence of contralateral breast cancer (two-sided significance test $2P=0.00001$).

Tamoxifen causes a wide range of adverse events which are distressing if not life threatening. There has been increasing concern

Table 2: Studies on the combination of radiotherapy and chemotherapy or tamoxifen

Author	Patient population		Treatment	Results
	Description	Number		
■ Overgaard for the Danish Breast Cancer Co-operative Group (1997) ¹⁰	Pre-menopausal high risk stage II and III patients, ie, tumours >5cm, node positive with skin or pectoral fascia invasion	1,708	50 Gray (Gy) in 25 fractions over five weeks and cyclophosphamide, 5-fluorouracil and methotrexate (CMF) for eight cycles versus CMF alone for nine cycles	Survival CMF alone 45% CMF and radiotherapy 54% $P<0.001$
■ Ragaz for the British Columbia Trial Eleven (1997) ¹¹	Pre-menopausal node positive patients	318	Multi-field radiotherapy delivering a total of 35Gy and CMF versus CMF alone	Survival Chemotherapy and radiation 64% Chemotherapy alone 54% $P<0.07$
■ Overgaard for the Danish Breast Cancer Co-operative Group (1999) ¹²	Post-menopausal high risk stage II and III patients	1,375	Local-regional radiotherapy plus tamoxifen versus tamoxifen alone	Survival Tamoxifen alone 36% Tamoxifen and radiation 45% $P<0.03$

over the risk of women developing endometrial cancer. The overview showed that women who had received tamoxifen were 2.58 times more likely to develop endometrial cancer. It extracted these data from the three largest trials containing tens of thousands of years follow-up data. This showed 42 cases of endometrial cancer in the treated group compared with nine in the untreated group. The same studies, when examined for contra-lateral breast cancer, showed 91 cases in the tamoxifen group compared with 157 in the non-tamoxifen group. These risks and benefits to tamoxifen should be discussed with patients.

I should express one word of caution regarding adjuvant tamoxifen treatment as a result of my own (unpublished) study of compliance in women in routine clinical practice receiving five years' treatment. This revealed that women take drug holidays of varying duration from two or three days to over a month, predominantly because of the oestrogenic effects, ie, flushes, sweats, weight gain, etc. The effect of this in the 150 women in my study was that their mean drug holiday in any 12 months was 1.9 months (57 days) or just under a year in a five year course.

The latest addition to the adjuvant hormonal treatment debate is the improvement offered by the addition of aromatase inhibitors (eg, anastrozole, letrozole) to this package of treatment. In one study, five years of anastrozole was compared with five years of tamoxifen. Disease-free survival was better in the anastrozole arm, and the incidence of adverse effects was also lower.¹⁵ An alternative strategy has been used in a trial where patients who have already received tamoxifen for five years are given letrozole for five years. Again, disease-free survival was improved for the patients receiving the aromatase inhibitor.¹⁶ A concern with both trials is the issue of lowered bone mineral density in the patients receiving long-term aromatase inhibitor therapy.

ADJUVANT CHEMOTHERAPY

The study that probably established the role of adjuvant chemotherapy was that conducted by Bonadonna and colleagues in 1976.¹⁷ This study also launched the most famous chemotherapy regimen of cyclophosphamide, methotrexate and 5-fluorouracil (CMF). Subsequently, many other regimens of CMF have been used, which differ slightly from "classic Bonadonna CMF". The evidence for the value of chemotherapy was cemented with the Oxford Overview in 1998, the meta-analysis of 18,000 women in 47 trials. At least 10 years' follow-up data were described.¹⁸ All of the trials compared a chemotherapy with non-chemotherapy regimen. The benefits seen by the Oxford Overview of chemotherapy in the prognostic group, described by age and nodal status, is presented in Table 4.

The Oxford Overview also contained an analysis of anthracycline therapy with 11 studies involving almost 6,000 women. These studies compared an anthracycline-containing arm with a non-anthracycline arm. This revealed a small but positive improvement of about 3 per cent, both in terms of disease-free recurrence and overall survival. However, patients in the anthracycline arm experienced an increase in adverse events (eg, nausea, vomiting, stomatitis and alopecia). This result was soon supported by the Levine study in 1998 on 800 patients, which showed a 7 per cent absolute survival increase at five years for the anthracycline group.¹⁹ Although this study also showed an increased incidence of adverse events in patients receiving the anthracycline, it was predictable and there was no evidence of cardiotoxicity. Many of these early studies had used anthracycline regimens based on doxorubicin. It is, however, well documented that epirubicin has a better cardiotoxicity threshold, which gives the potential for higher dosing of the anthracycline. This avenue that may be highly beneficial if the data from the GFEA-05 study are confirmed. This 565 patient GFEA-05 study compared cyclophosphamide, epirubicin 50mg/m² and 5-fluorouracil (CEF-50) with the same dose of cyclophosphamide and 5-fluorouracil, but with the epirubicin dose doubled to 100mg/m² (CEF-100). The study showed an 11 per cent improvement in the five-year survival ($P=0.007$) in the CEF-100 group.²⁰

Further evidence to support the role of epirubicin was provided by the combined analysis of the National Epirubicin Adjuvant Trial (NEAT) and Scottish Cancer Trials Breast Group BR9601 studies presented at

the American Society of Clinical Oncology (ASCO) meeting in 2003.²¹ Here four cycles of epirubicin 100mg/m² followed by four cycles of CMF were compared with eight cycles of CMF alone. These studies contained 2,391 patients and showed an improvement in relapse-free survival of 22 months with a hazard ratio of 0.69 ($P<0.0001$) in favour of the epirubicin and CMF sequential regimen. Patients were followed-up for five years.

The final part of the adjuvant chemotherapy story is the value of the recently licensed taxanes. The evidence for their benefit comes from three large randomised studies: Cancer and Leukemia Group B (CALGB)-9344 (n=3,121),²² the National Surgical Adjuvant Breast and Bowel Project (NSABP)-B28 (n=3,059)²³ and Breast Cancer International Research Group (BCIRG)-001 (n=1,491).²⁴ The CALGB and NSABP studies are both paclitaxel studies, which consider the sequential addition of four cycles of paclitaxel to the standard doxorubicin, cyclophosphamide regimen (AC), whereas the BCIRG-001 study substituted docetaxel into the AC combination and compared it with 5-fluorouracil, doxorubicin and cyclophosphamide (FAC).

The results of the CALGB study, presented at the ASCO meeting in 2002, showed that with over five years follow-up the sequential combination delivered a 17 per cent reduction in the risk of recurrence and an 18 per cent reduction in the risk of death. The NSABP study did not report until ASCO 2003 and differed from the CALGB study in having far fewer high-risk patients. It still showed a benefit to the paclitaxel arm in terms of disease-free survival ($P=0.008$), but only a trend to better overall survival in the paclitaxel arm ($P=0.46$). The BCIRG-001 data are even less mature, with data for disease-free survival only being available for three years. Disease-free survival was 82 per cent in patients receiving docetaxel, doxorubicin and cyclophosphamide (TAC) and 74 per cent in those receiving FAC ($P=0.0022$). Therefore there seems little doubt that a taxane should be added to adjuvant chemotherapy regimens.

A further question, which has been indirectly answered by all of the studies, revolves

Table 3: Mortality reduction in early breast cancer patients receiving tamoxifen

Duration	ER positive	ER unknown
1 year	14%	10%
2 years	18%	15%
5 years	28%	21%

Table 4: Results from the Oxford Overview on the value of chemotherapy

Age	Nodal status	Absolute reduction in recurrence (%)	Absolute reduction in all causes mortality (%)
Under 50 years	+ve	15.4	12.4
	-ve	10.4	5.7
50-69 years	+ve	5.4	2.3
	-ve	5.7	6.4

around duration and sequencing of chemotherapy. The 1998 Oxford Overview reported on 11 randomised trials involving 6,104 patients receiving polychemotherapy.¹⁸ They were divided into those that had received treatment of greater than six months' duration and less than six months' duration. Longer chemotherapy conferred a reduction in recurrence but only a 1 per cent (non-significant) benefit in terms of improved survival. Both the anthracycline trials such as NEAT and the taxane trials such as CALGB along with numerous small studies suggest that benefits of multi-drug chemotherapy are maximised when sequential schedules are employed over combination or alternating schedules.

There are some questions about adjuvant chemotherapy (the studies have been or are being done and the answers will become available over the next two to five years) which remain:

- The role of trastuzumab in Her-2 positive patients, both in terms of effect and optimal duration. This is being considered in the Herceptin Adjuvant (Her-A) study.
- The addition of further agents to anthracycline or taxane-based chemotherapy, the most exciting of which is probably gemcitabine, which shows synergy with paclitaxel in the advanced stage of breast cancer.
- Whether 5-fluorouracil in the form of oral capecitabine is an improvement on historic 5-fluorouracil based regimens.
- The sequencing of adjuvant radiotherapy relative to adjuvant chemotherapy.

— FOR THE FUTURE

There are numerous epidermal and vascular growth factor receptor inhibitors as well as the proteasome inhibitor bortezomib which have all shown benefit in the treatment of breast cancer. Definitive phase III trials are under way and we await completion, analysis and results.

This article has deliberately not considered the chemotherapy of metastatic disease as it warrants an article in its own right. However, it is important to remember that the drugs which have been mentioned in the early disease context all have activity and therefore a role in the treatment of metastatic disease

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