Leading Article

Recent advances in the treatment of breast cancer

W.J.B. Smellie and N.P.M. Sacks

Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK

Introduction

There are 25,000 new cases of breast cancer diagnosed annually in the UK, resulting in 15,000 deaths; two thirds of these cases occur in women over the age of 50.¹ The treatment of breast cancer has changed greatly over the last 20 years, resulting in a modest improvement in long-term survival, associated with considerable reductions in the extent of local surgery routinely performed for this disease. Sadly these improvements are balanced by a world-wide increase in the incidence of the disease and therefore the mortality rates have remained static.² These improvements have not come about serendipitously but as a result of extensive painstaking laboratory work and international randomized controlled clinical trials. Undoubtedly the most significant survival benefits for women with early breast cancer have resulted from the widespread use of adjuvant endocrine therapy and cytotoxic chemotherapy. The Breast Cancer Trialists Collaborative Group overview analysis of 75,000 women enrolled world-wide in 133 clinical trials clearly demonstrated a risk reduction in the odds of death and relapse with the use of adjuvant therapy, in addition to appropriate local treatment, of approximately 30%.³ Few physicians would now consider surgical treatment alone to be adequate for most patients with invasive breast cancer.

Demands for less extensive surgery have led to trials addressing the question of survival and local recurrence rates associated with conservative surgery, with the aim of allowing preservation of body-image without sacrificing longevity. It has now been conclusively shown that, in selected cases, breast-conserving surgery in combination with radiotherapy provides adequate local control with identical survival to that achieved with mastectomy.⁴ Unfortunately breast conservation has not led to the hoped-for improvement in quality of life and reduction in anxiety and depression.⁵ Further developments in local breast cancer

treatment must now fine-tune the indications for such surgery and optimize the radiotherapy requirements whilst awaiting a fundamental breakthrough in systemic therapy approaches.

Familial breast cancer and primary chemoprevention

Perhaps the most significant recent advance in discovering the aetiology of breast cancer has been the identification of the BRCA1 gene locus on chromosome 17q associated with familial breast and ovarian cancer, which is inherited as an autosomal dominant trait. The presence of this gene confers a risk of 59% for the development of breast cancer by the age of 50 and 82% by the age of 70.⁶ Not only does this provide a valuable insight into the basic pathogenesis of breast cancer, but may also mean in the future that susceptible individuals can be identified before the onset of the disease and offered prophylactic surgery. Of course this approach opens up enormously complex moral and ethical issues. Unfortunately more than 90% of breast cancers occur sporadically, with about a third of the rare cases between the ages of 20–29 having a genetic basis, dropping to 1% by the age of 80⁷ so that widespread screening for this gene and other genetic abnormalities associated with increased susceptibility will not have any impact on the vast majority of women that develop the disease in the absence of a positive family history.

The best form of 'therapy' for any disease and particularly cancer is its prevention. The two methods available for breast cancer are attempted primary chemoprevention of individuals at increased risk such as by the use of tamoxifen and secondary prevention of the disease by diagnosis at an early, impalpable stage using screening mammography. There is currently a large pilot randomized prospective placebo-controlled study of tamoxifen in patients with a strong family history of breast cancer or other risk factors at the Royal Marsden Hospital, which has accrued over 2,000 patients⁸ and similar phase III trials are under way in the United States and Europe. The results of

Correspondence and reprints: N.P.M. Sacks, M.S., F.R.A.C.S., St George's Hospital, Blackshaw Road, London SW17 0QT, UK.

Received: 21 October 1993

these, however, will not be available for a number of years because of the small number of expected events. The trial is justified on extensive experimental data and the clinical observation that tamoxifen reduces the incidence of contralateral breast cancers in patients with previous breast cancer by 40%³ and can therefore be regarded as potentially prophylactic. Experimental studies have shown that tamoxifen reduces the incidence of primary breast cancer and 7,12-dimethylbenzanthracene-induced breast cancer in rats.⁹ A further potential class of agents for chemoprevention that is being assessed are compounds based on retinoic acid (retinoids) which are effective in reducing the incidence of breast cancer in animals by inducing cancer differentiation.¹⁰ There is a prevention trial under way using the synthetic drug fenretinide, that has less of the hepatotoxic side effects that characterize this group of compounds.¹¹

Breast screening

Whilst the vast majority of cancers detected by modern screening mammography programmes are small invasive well-differentiated carcinomas, it is not clear that all women benefit from the screening programme. The recent results of the Swedish overview of the randomized studies¹² and the 10-year results of the UK study¹³ confirm that there is a definite survival advantage of screening women in certain age-groups only. The UK trial compared women in the age groups 45–64 years invited for mammographic breast screening, and showed a reduction in the risk of death of 20% compared with the unscreened controls. The Swedish overview, which involved a meta-analysis of five randomized trials of 282,777 women, followed for 5–13 years, showed a highly significant 24% reduction in breast cancer mortality in women invited to attend for screening, with the greatest benefit of screening seen in the 50–59 year age groups and a non-significant 13% reduction in mortality observed in 45–49 year old age group. Therefore it would seem reasonable to continue mammographic screening of women after the age of 50, but there is no scientific evidence that there is any benefit under this age. Approximately 20% of the cancers picked up as a part of the mammographic screening programme prove to be pre-invasive ductal carcinoma *in situ* (DCIS). Prior to screening this was an uncommon entity and, although there is not a universally accepted risk factor for the subsequent development of invasive breast cancer from untreated DCIS, it is thought to be 30–50% of cases,¹⁴ although this depends on the grade of the DCIS.¹⁵ Having demonstrated a suspicious pattern of calcification on mammogram, needle-guided localization biopsy is per-

formed to confirm the diagnosis, followed by complete excision of the area of *in situ* disease.

Treatment of breast cancer

Intense controversy exists as to the most appropriate adjuvant therapy following surgery. The results of the UKCCR, BASO and EORTC trials are not yet available: however, the recently reported NSABP trial suggested that the event-free survival rate was significantly increased in the patients who received radiotherapy to the breast as well as complete local excision of DCIS,¹⁶ follow-up, however, is short with a mean of 43 months. Multifocal or very extensive DCIS is thought to have a greater invasive potential and is probably best treated by mastectomy with or without immediate reconstruction, which is becoming more widespread, reflecting an increase in the numbers of surgeons that can offer the technique coupled with the knowledge that it does not have any detrimental effect on the patient's tumour or its subsequent treatment.¹⁷ The role of tamoxifen in patients with complete excision of DCIS is uncertain and the focus of the studies mentioned above.

The standard initial treatment for early breast cancer is surgery, although primary treatment of breast cancer with tamoxifen has been evaluated extensively as a treatment option in the elderly. The results of the recent Cancer Research Campaign trial, however, show that patients over the age of 70 initially treated with tamoxifen have the same survival rates as those treated by surgery followed by adjuvant tamoxifen, although the former treatment fails in two thirds of cases and the patients then have to undergo surgery at an older age.¹⁸

The endocrine therapy of metastatic breast cancer has also changed with the appearance of alternatives to tamoxifen and progestogens. This has been eagerly awaited since 30% of patients who initially respond to endocrine therapy with tamoxifen relapse due either to primary endocrine resistance or pure tamoxifen resistance.¹⁹ The new aromatase inhibitor 4-hydroxyandrostenedione, which prevents peripheral conversion of androgens to oestradiol, has a similar response rate in patients with advanced disease as tamoxifen²⁰ and is effective in patients with secondary tamoxifen resistance.²¹ A great deal of work has been devoted to targeted therapy using monoclonal antibodies directed against breast cancer antigens;²² however, much more work remains to be done to overcome problems associated with this approach before this technique can be clinically applicable.

Debate continues about the most appropriate treatment for the axilla in patients with early breast cancer.²³ The Danish Breast Cancer Cooperative group recently published their findings, showing

that adequate local therapy of the axilla, which involved level I and II dissection, not only reduced local recurrence rates but also increased survival.²⁴ The morbidity of this procedure and prolonged hospital stay are considered unacceptable by some surgeons, who would prefer to offer radiotherapy to the axilla, which has similar short-term morbidity to surgery alone, although the combination must be avoided at all costs. Avoidance of axillary surgery means that the prognostic information that could have been gained from the axillary lymph nodes is lost, making it more difficult both to select the patients that will benefit the most from adjuvant chemotherapy and to counsel the patient appropriately. In patients with negative axillary nodes there is now an ever-increasing number of tumour-related prognostic markers available, such as EGFR, c-erbB2, proliferation and angiogenesis factors.²⁵ It is hoped that the clinician is then able to select those node-negative patients at greatest risk of relapse who should be given adjuvant chemotherapy. The underlying assumption, as yet unproved, is that it is these same patients who derive the greatest benefit of adjuvant therapy, whilst those at low risk receive no benefit. Whilst of enormous research interest, few new prognostic indicators are currently in widespread clinical use and what are more urgently needed are tumour factors predictive of response and resistance to treatment; unfortunately there are all too few of these. The presence of oestrogen and progesterone receptors, to an extent, predicts response to endocrine therapy in early and advanced disease.²⁵ However, the fact that even receptor-negative tumours can respond to endocrine therapy means endocrine receptor status alone is not routinely used in this country to decide whether the patient should receive tamoxifen. The c-erbB2 proto-oncogene product is only expressed in around 15% of breast tumours; however, it is a predictor of poor response to hormonal therapy²⁶ and chemotherapy,²⁷ and therefore is an attractive receptor target for new biological therapies.²⁸

The emphasis of current chemotherapy trials has shifted away from testing different drug combinations towards trials of primary chemotherapy or chemotherapy given both before and after surgery for operable breast tumours (neoadjuvant chemotherapy). Whilst there is an experimental rationale for such therapy showing reduction in the release of

growth factors from tumour deposits,²⁹ current trials are examining whether this approach could result in prolonged survival in humans. The recently updated Milan trial confirms that neoadjuvant chemotherapy can radically reduce the number of patients that require mastectomy to achieve adequate local tumour removal.³⁰ However, there is no evidence to date of improvement in survival with neoadjuvant as opposed to conventional adjuvant treatment given after surgery. The long-term results of the Milan trial and other trials, such as that under way at the Royal Marsden Hospital,³¹ are awaited with great interest. Complete remission of metastatic tumours has been achieved using high-dose chemotherapy regimens with autologous bone marrow transplant in some cases.³⁰ However, sustained disease-free survival has been rare and in fact convincing evidence of a positive dose response relationship in breast cancer is lacking.³² Some groups have now applied this approach of high-dose adjuvant therapy to those patients adjudged to have a very poor prognosis and the preliminary results are very encouraging.³³

Conclusions

Currently almost all aspects of the prevention and treatment of breast cancer are actively being investigated, from the developmental biology of the breast to the treatment of advanced metastatic disease. It must not be forgotten that the national mortality of breast cancer has remained static because advances in the treatment of the disease and prolonged life expectancy of sufferers is balanced by an increased incidence of new cases.³⁴ Either preventing or treating the cause of this increased incidence will therefore have the same effect as all the other advances in therapy that have been made this century. Rather than to continue our march down the same path perhaps it is time to re-evaluate our conceptual biological approach to breast cancer, consider new treatment approaches and make a paradigm shift in our understanding of the disease process.³⁵ Any advances in the treatment of breast cancer must be proven by prospective randomized clinical trials and not only must facilities be available for these to take place, but clinicians are to be strongly encouraged to enter patients into such series.

References

1. La Vecchia, C.L., Lucchini, F., Negri, E., Boyle, P., Maisonneuve, P. & Levi, F. Trends of cancer mortality in Europe, 1955-1989: 111, breast and genital sites. *Eur J Cancer* 1992, **28A**: 927-998.
2. Harris, J.R., Lippman, M.E., Veronesi, U. & Willett, W. Breast cancer. *N Engl J Med* 1993, **327**: 319-328, 390-398, 473-480.
3. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. *Lancet* 1992, **339**: 1-15, 71-85.
4. Fisher, B., Redmond, C., Poisson, R. *et al.* Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 1989, **320**: 822-828.

5. Schain, W. & Fetting, J.H. Modified radical mastectomy versus breast conservation: psychosocial considerations. *Semin Oncol* 1993, **19**: 239–243.
6. Easton, D.F., Bishop, D.T., Ford, D., Crockford, G.P. & the Breast Cancer Linkage Consortium. Genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. *Am J Hum Genet* 1993, **52**: 678–701.
7. Claus, E.B., Risch, N.J. & Thompson, W.D. Genetic analysis of breast cancer in the cancer and steroid hormone study. *Am J Hum Genet* 1991, **48**: 232–242.
8. Powles, T.J., Tillyer, C.R., Jones, A. *et al.* Prevention of breast cancer with tamoxifen – an update of the Royal Marsden Hospital pilot programme. *Eur J Cancer* 1990, **26**: 680–684.
9. Jordan, V.C., Lababidi, M.K. & Langan-Fahey, S. Suppression of mouse mammary tumorigenesis by long-term tamoxifen therapy. *J Natl Cancer Inst* 1991, **83**: 492–496.
10. Ratko, T.A., Detrisac, C.J., Dinger, N.M., Thomas, C.F., Kelloff, G.J. & Moon, R.C. Chemopreventive efficacy of combined retinoid and tamoxifen treatment following surgical excision of a primary mammary cancer in female rats. *Cancer Res* 1989, **49**: 4472–4476.
11. Formelli, F., Clerici, M., De Palo, G., Costa, A. & Veronesi, U. Chronic oral administration of fenretinide, as a chemopreventive agent to breast cancer, does not affect plasma alpha-tocopherol concentration. *Ann Oncol* 1992, **2**: 446–447.
12. Nystrom, L., Nystrom, L.R., Wall, S. *et al.* Breast cancer screening with mammography: overview of Swedish randomised trials. *Lancet* 1993, **341**: 973–978.
13. UK Trial of Early Detection of Breast Cancer Group. Breast cancer mortality after 10 years in the UK trial of early detection of breast cancer. *Breast* 1993, **2**: 13–20.
14. Fentiman, I. Ductal carcinoma in situ. *Br Med J* 1992, **304**: 1261–1262.
15. Bellamy, C.O.C., McDonald, C., Slater, D.M., Chetty, U. & Anderson, T.J. Noninvasive ductal carcinoma of the breast: the relevance of histologic categorization. *Hum Pathol* 1993, **24**: 16–23.
16. Fisher, B., Constantino, J., Redmond, C. *et al.* Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer. *N Engl J Med* 1993, **328**: 1581–1586.
17. Johnson, C.H., van Heerden, J.A., Donohue, J.H., Martin, J.K., Jackson, I.T. & Ilstrup, D.M. Oncological aspects of immediate breast reconstruction following mastectomy for malignancy. *Arch Surg* 1989, **124**: 819–824.
18. Bates, T., Houghton, J., Fallowfield, L. & Baum, M. Breast cancer in elderly women: a Cancer Research Campaign trial comparing treatment with tamoxifen and optimal surgery with tamoxifen alone. *Br J Surg* 1991, **78**: 591–594.
19. Johnston, S.R., Dowsett, M. & Smith, I.E. Towards a molecular basis for tamoxifen resistance. *Ann Oncol* 1992, **3**: 503–511.
20. Coombes, R.C., Hughes, S.W.M. & Dowsett, M. 4-Hydroxyandrostenedione: a new treatment for postmenopausal patients with breast cancer. *Eur J Cancer* 1992, **28A**: 1941–1945.
21. Stein, R.C., Dowsett, M., Hedley, A. *et al.* Treatment of advanced breast cancer in postmenopausal women with 4-hydroxyandrostenedione. *Cancer Chemother Pharmacol* 1990, **26**: 75–78.
22. DeNardo, S.J., Warhoe, K.A., O'Grady, L.F. *et al.* Radioimmunoassay for breast cancer: treatment of a patient with I131 L6 chimeric monoclonal antibody. *Int J Biol Mark* 1991, **6**: 221–230.
23. Sacks, N.P.M., Barr, L.C., Allan, S.M. & Baum, M. The role of axillary dissection in operable breast cancer. *The Breast* 1992, **1**: 41–49.
24. Axelsson, C.K., Mouridsen, H.T. & Zedeler, K. Axillary dissection of level I and II lymph nodes is important in breast cancer classification. *Eur J Cancer* 1992, **28A**: 1415–1418.
25. Gasparini, G., Pozza, F. & Harris, A.L. Evaluating the potential usefulness of new prognostic and predictive indicators in node-negative breast cancer patients. *J Natl Cancer Inst* 1993, **85**: 1206–1209.
26. Wright, C., Nicholson, S., Angus, B. *et al.* Relationship between c-erbB2 protein product expression and response to endocrine therapy in advanced breast cancer. *Br J Cancer* 1992, **65**: 118–121.
27. Gusterson, B.A., Gelber, R.D., Goldhirsch, A. *et al.* Prognostic importance of c-erbB2 expression in breast cancer. *J Clin Oncol* 1992, **10**: 1049–1056.
28. Lippman, M.E. The development of biological therapies for breast cancer. *Science* 1993, **259**: 631.
29. Gunduz, N., Fisher, B. & Saffer, E.A. Effect of surgical removal on the growth and kinetics of residual tumor. *Cancer Res* 1979, **39**: 3861–3865.
30. Bonadonna, G. Evolving concepts in the systemic treatment of breast cancer. *Cancer Res* 1992, **52**: 2127–2137.
31. Powles, T.J., O'Brien, M.E.R., Hickish, T.F. *et al.* The effect of preoperative (neoadjuvant) chemotherapy on the requirement for mastectomy for treatment of primary breast cancer. *Eur J Cancer* 1993 (in press).
32. Dodwell, D.J. Cytotoxic drugs: the search for dose-response. *Lancet* 1993, **341**: 614.
33. Peters, W.P. High-dose chemotherapy and autologous bone-marrow support in the treatment of metastatic and primary breast cancer. *The Breast* 1993, **2**: 110–114.
34. Sacks, N.P.M. Biological basis of adjuvant systemic therapy for early breast cancer. In: Salmon, S.E. (ed.) *Adjuvant Therapy of Cancer*, 7th edn. J.B. Lippincott Co., 1993, pp. 34–42.
35. Baum, M. Cancer 2000 BC to 2000 AD – time for a paradigm shift? *Acta Oncol* 1993, **32**: 3–8.