therapy might have a role in the management of much smaller early breast cancers amenable to conservative surgery. Here the justification for such treatment would be improved survival. Studies in experimental tumour systems have shown that non-curative surgery or radiotherapy is associated with stimulation of residual tumour cell growth by a serum growth factor; prior treatment with chemotherapy or tamoxifen suppresses this effect and prolongs survival [7, 8]. A large randomised clinical trial in the U.S.A. and Canada is currently underway to determine whether primary medical chemotherapy will prolong disease-free survival and survival more effectively than the same chemotherapy given postoperatively (NSABP protocol B-18). A similar pilot trial is underway at the Royal Marsden Hospital. Results are not yet available from either of these trials.

1. Rubens RD, Bartelink H, Englesman E, *et al.* Locally advanced breast cancer: the contribution of cytotoxic and endocrine treatment to radiotherapy. *Eur J Cancer Clin Oncol* 1989, 25, 667–678.
2. Haagensen CD, Bodian C. A personal experience with Halsted's radical mastectomy. *Ann Surg* 1984, **199**, 143–150.
3. Hayward LJ, Carbone PP, Hewson J-C, *et al.* Assessment of response to therapy in advanced breast cancer. *Br J Cancer* 1977, **39**, 1289–1294.
4. Jodrell DI, Smith IE, Mansi JL, *et al.* A randomised comparative trial of mitoxantrone, methotrexate, mytomycin C (MMM) and cyclophosphamide, methotrexate and 5-FU (CMF) in the treatment of advanced breast cancer. *Br J Cancer* 1991, **63**, 794–798.
5. Anderson EDC, Forrest APM, Hawkins RA, Anderson TJ, Leonard RCF, Chetty U. Primary systemic therapy for operable breast cancer. *Br J Cancer* 1991, **63**, 561–566.
6. Bonadonna G, Veronesi U, Brambilla C, *et al.* Primary chemotherapy to avoid mastectomy in tumours with diameters of three centimetres or more. *J Natl Cancer Inst* 1990, **82**, 1539–1545.
7. Fisher B, Saffer EA, Rudock C, *et al.* Presence of a growth stimulating factor in serum following primary tumour removal in mice. *Cancer Res* 1989a, **49**, 1996–2001.
8. Fisher B, Saffer EA, Rudock C, *et al.* Effect of local or systemic treatment prior to primary tumour removal on the production and response to a serum growth stimulating factor in mice. *Cancer Res* 1989b, **49**, 2002–2004.

Eur J Cancer, Vol. 29A, No. 4, pp. 595–598, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00
Pergamon Press Ltd

Adjuvant Systemic Therapy in Breast Cancer

H.T. Mouridsen

Systemic adjuvant therapy has improved the prognosis of patients with primary breast cancer. Meta-analyses have demonstrated that approximately one fourth of deaths can be avoided among younger women treated with multiple cytotoxic drug regimens and among older women treated with tamoxifen. However, with the treatments available today many aspects related to the optimal therapy, taking into account the physical, psychological and socioeconomic consequences, are still open. This review discusses some of the major open questions related to the effectiveness of the adjuvant systemic therapy in terms of its ability to reduce recurrence rate and mortality.
Eur J Cancer, Vol. 29A, No. 4, pp. 595–598, 1993.

INTRODUCTION

RADICAL LOCOREGIONAL therapy fails to cure approximately 70% of patients presenting with breast cancer [1]. It is now well recognised that subclinical metastases are often established before the clinical detection of breast cancer and therapy directed at the primary tumour fails to affect these metastases.

This is the rationale for adjuvant systemic therapy which was introduced approximately 20 years ago. Until the mid-1980s, however, there was conflicting evidence about the benefit of adjuvant systemic therapy, but the results of the updated meta-analyses of the Early Breast Cancer Triallists Collaborative Group [2, 3] have now ended the dispute about the benefit in terms of reduction of recurrence rate and mortality. In brief, these analyses have demonstrated a highly significant relative reduction in recurrence rates by about 25% and a slightly lower mortality reduction with tamoxifen in patients 50 years old or more and with polychemotherapy or ovarian ablation in patients less than 50 years. Furthermore, direct randomised comparisons have demonstrated polychemotherapy to be superior to single-agent therapy and long-term chemotherapy to be no better than shorter (6 months) regimens.

Thus the introduction of adjuvant systemic therapy has led to an advance in the treatment of breast cancer although it is evident that with the treatments availble today we are far from having achieved a dramatic improvement in the prognosis of breast cancer.

Many questions regarding the optimal therapy, taking into account on the one hand, efficacy and on the other hand, the physical, psychological and socioeconomic consequences, are still open and subject to present and future analysis in clinical trials.

In the following, some of the questions related to efficacy in terms of reduction in recurrence rate and mortality will be addressed.

ENDOCRINE THERAPY

Duration of tamoxifen

Indirect comparisons [2] have indicated that 2 years or even 5 years of adjuvant tamoxifen may be superior to shorter tamoxifen regimens and even outside clinical trials prolonged tamoxifen is now widely used. However, it should be emphasised that the optimal duration needs to be defined from the results of randomised trials and several studies to analyse the importance of duration are now in progress. These trials should also carefully

Correspondence to H.T. Mouridsen, Department of Oncology 5074, Rigshospitalet, 9 Blegdamsvej, 2100 Copenhagen Ø, Denmark.
Received and accepted 7 Sep. 1992.
EJC 29:4-F

analyse other potential long-term benefits, such as osteoporosis, ischaemic heart disease [4–7] or potential harm such as endometrial cancer [8, 9] with prolonged therapy.

Ovarian ablation/tamoxifen in premenopausal patients

As mentioned, the meta-analyses have demonstrated that adjuvant castration leads to a reduction in mortality similar to that observed with chemotherapy. On the contrary, no significant benefit has been observed so far with adjuvant tamoxifen. However, the number of premenopausal patients on tamoxifen in randomised trials is rather small and the majority have received the tamoxifen in addition to chemotherapy (i.e. chemotherapy vs. chemotherapy plus tamoxifen).

Furthermore, chemotherapy-related ammenorhea has been associated with superior disease-free survival in some trials although not in others [10] and this has led to speculations that the effects of adjuvant chemotherapy may be mediated by suppressing ovarian function.

These observations have renewed the interest of adjuvant endocrine therapy in premenopausal patients and studies are now in progress comparing chemotherapy with castration or tamoxifen or leutinising hormone-releasing hormone (LHRH) analogues. Preliminary data are conflicting and have demonstrated chemotherapy [cyclophosphamide, methotrexate, 5-fluorouracil (CMF) 6 months] to be superior to tamoxifen (2 years) in premenopausal node-positive receptor-positive patients [11], whereas no difference was observed in another trial comparing castration plus tamoxifen for 2 years with chemotherapy (mitomycin C plus cyclofosfamide) [12].

Combined endocrine therapy

With the exception of tamoxifen combined with prednisolone, a series of randomised trials in advanced disease have demonstrated similar therapeutic gain with tamoxifen compared with tamoxifen in combination with other endocrine agents [13].

However, the alternating endocrine approach (i.e. treatment with one endocrine agent followed by treatment with another endocrine agent) could be applied in the adjuvant setting. The rationale for this approach is the demonstration of partial cross-sensitivity and partial non-cross resistance between treatment with tamoxifen and other endocrine agents. Thus, in patients having responded to first-line tamoxifen, the chance of subsequent response to another endocrine agent is 42%, and in patients failing first-line therapy with tamoxifen, approximately 15% will respond to second-line endocrine therapy [13].

So far, alternating treatment with tamoxifen and medroxyprogesterone-acetate (MPA) has been analysed in four trials. In three of the trials tamoxifen and MPA were alternated every second week [14]. The rate of response and other treatment end-points were similar for the combination and for tamoxifen alone. Since the half-life of tamoxifen exceeds 2 weeks, it can be argued that the lack of an additive effect of the alternating approach is due to pharmacodynamic interaction at the receptor level. Preliminary results from a trial comparing tamoxifen alone with tamoxifen alternating with MPA every 8 weeks have been presented [15]. A total of 199 patients, known to be oestrogen-receptor positive have been included in the trial, and so far 95 patients are evaluable. The response rates are 68 and 45% in tamoxifen/MPA- and tamoxifen-treated patients, respectively. It is noteworthy that the increased overall response rate is due to an increase in the rate of complete remission. These results encourage a further exploration of alternating endocrine modalities in the adjuvant setting and the questions to be addressed include durations, numbers and sequences of the different endocrine therapies.

Intermittent endocrine therapy

Hormone deprivation of hormone-dependent tumours may enhance the process of dedifferentiation to autonomy. This is suggested by several experiments [16–18] in which oestrogen-dependent breast tumours rapidly became autonomous when transplanted into an oestrogen-free host. The most interesting experiments in this context showed that partial replacement of oestrogens or androgens, after deprivation of these hormones in experimental hormone-dependent mammary or prostatic cancer, slowed down the progression to autonomy [18, 19].

The intermittent approach is now being tested in a randomised EORTC trial in advanced disease [20] but should also be tested in primary disease to answer the important question of the possible postponement of development from hormone dependency to hormone independency.

CHEMOTHERAPY

Use of anthracyclines

In advanced breast cancer, the anthracyclines (doxorubicin/epirubicin) are the single most active agents and randomised comparisons between CMF or regimens substituting methotrexate by doxorubicin [14] have demonstrated the anthracycline-containing regimens generally to be superior with respect to the major end-points: response rate, median duration of response and survival.

These data have stimulated the evaluation of the role of anthracyclines in the adjuvant setting. In the NSABP trial B-11 [21] patients less than 49 years or aged 50–59 with negative receptors were randomised to PF (melphalan + 5-fluorouracil) or to PF plus doxorubicin. At 6 years the anthracycline-treated patients had longer recurrence-free survival and survival. However, the superiority could also be attributed to the superiority of a three-drug compared to a two-drug combination.

In another trial comparing CMF with CAFV (cyclophosphamide, doxorubicin, 5-fluorouracil, vincristine) [22] a small subset of premenopausal patients with node-negative disease did better on the CAFV regimen. However, apart from the doxorubicin, the cyclophosphamide and 5-fluorouracil schedules also differed in the two regimens.

Three other trials failed to demonstrate any difference. The NSABP trial which compared PF and tamoxifen (PFT) to PAFT in patients over the age of 60 years or patients aged 50–59 with positive receptors [21], the Milan trial which compared CMF × 12 with CMF × 8 followed by doxorubicin for four cycles [23] and the NSABP trial which compared four cycles of doxorubicin and cyclophosphamide (AC) with six cycles of CMF [24].

Thus no firm conclusions can yet be drawn and the question should be further analysed in randomised trials with regimens designed properly to identify the exact role of the anthracyclines. The trials should also carefully analyse any long-term side-effects especially with regard to cardiotoxicity.

Dose/response relationships

Hryniuk and Levine [25] emphasised the importance of dose intensity and when they correlated 3 years disease-free survival with dose intensity there was a significant positive correlation. However, these analyses are based on a number of assumptions which may invalidate the conclusions. Retrospective analyses of chemotherapy dose and disease-free survival in individual trials

did not confirm the dose–response relationship as recently reviewed by Henderson *et al* [26]. Among 15 trials analysing the recurrence-free survival or survival according to dose level higher or lower than 75–90% of the scheduled dose, seven demonstrated the existence of a dose–response relationship, whereas eight did not, and in two of the last trials the low dose group actually did significantly better.

In advanced disease several prospective trials have addressed the questions of dose [14] but so far, no firm conclusions can be drawn. In the adjuvant setting randomised trials are now ongoing, some of which are using different ways to protect the bone marrow to allow significant dose escalation (haemopoetic growth factors, autologous bone marrow rescue), but so far no conclusive data are available.

COMBINED CHEMOTHERAPY AND ENDOCRINE THERAPY

Premenopausal patients

Two trials compared ovarian ablation plus chemotherapy with chemotherapy alone. One trial compared oophorectomy plus CMFP with the same chemotherapy in premenopausal patients with node-negative disease [27]. At 8 years patients who were oestrogen receptor positive did better on the combination as far as disease-free survival is concerned. The other trial [28] compared CMF + ovarian irradiation to CMF alone in patients with node-positive receptor-positive disease. At 8 years the disease-free survival favoured the combination. In none of these two trials was a survival benefit achieved with the addition of ovarian ablation.

Other trials compared chemotherapy with chemotherapy plus tamoxifen [29–32]. So far no significant improvement of survival has been observed from the combination. Indeed, in the NSABP trial [30] a retrospective subgroups analysis revealed a difference in favour of the chemotherapy alone in patients with receptor-negative disease and in the Danish trial early data on survival indicated that the chemoendocrine group did significantly worse than those treated with CMF alone [32].

Trials are now ongoing evaluating the sequential use of chemotherapy and endocrine therapy in premenopausal patients.

Postmenopausal patients

One of the key questions in postmenopausal patients is whether chemotherapy added to endocrine therapy is beneficial. Several trials have compared a combined chemoendocrine approach with endocrine therapy alone [32–39]. Most of these have shown that the combination results in small improvements in disease-free survival, but not in overall survival. However, in one trial [38] four cycles of AC plus tamoxifen for 5 years was significantly better than tamoxifen alone for 3 years (disease-free survival and survival) in patients over the age of 60 or patients aged 50–59 years with receptor-positive tumours.

More mature data from the ongoing trials must be generated to enable further conclusions.

TREATMENT OF NODE-NEGATIVE DISEASE

The definition of a node-negative disease depends upon the extent of the primary surgical approach in the axilla [40], but in general the fraction of patients with negative nodes will probably rise in the future as a result of the increased use of screening programmes for early breast cancer.

According to the meta-analyses the relative reduction of recurrence rate and mortality is similar in node-negative and node-positive disease.

However, approximately 70% of patients with node-negative tumours are cured after local therapies and, therefore, only 30% of the node-negative population could potentially benefit from adjuvant systemic therapy. Hence, there is a potentially significant problem of overtreatment as the result of a general use of systemic therapy for node-negative disease.

It is, therefore, mandatory to develop factors which can identify the patients among those with negative tumours who are at high risk of developing recurrence (prognostic factors) and factors to select the patients for treatment according to the probability of response to that specific therapy (predictive factors).

1. Brinkley D, Haybittle J. The curability of breast cancer. *Lancet* 1975, ii, 95–97.
2. Early Breast Cancer Triallists Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. *Lancet* 1982, **339**, 1–15.
3. Early Breast Cancer Triallists Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. *Lancet* 1992, **339**, 71–85.
4. Smith I. Adjuvant tamoxifen for early breast cancer. *Br J Cancer* 1988, **57**, 527–528.
5. Powles TJ, Hardy JR, Ashley SE. A pilot study to evaluate the acute toxicity and feasibility of tamoxifen for prevention of breast cancer. *Br J Cancer* 1989, **60**, 126–131.
6. Fornander T, Rutqvist LE, Sjøberg HE, Blomqvist L, Mattson A, Glas U. Long-term adjuvant tamoxifen in early breast cancer: effect on bone mineral density in postmenopausal women. *J Clin Oncol* 1990, **8**, 1019–1024.
7. Love R, Mazess RB, Barden H, *et al*. Effect of tamoxifen on bone mineral density in postmenopausal women with breast cancer. *N Engl J Med* 1992, **326**, 852–856.
8. Fornander T, Rutqvist LE, Cedermark B, *et al*. Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancer. *Lancet* 1989, i, 117–120.
9. Andersson M, Storm HH, Mouridsen HT. Incidence of new primary cancers after adjuvant tamoxifen therapy and radiotherapy for early breast cancer. *J Natl Cancer Inst* 1991, **83**, 1013–1017.
10. Goldhirsch A, Gelber RD, Mouridsen HT. Adjuvant chemotherapy in premenopausal patients: a more complicated form of oophorectomy. In Cavalli F, ed. *Endocrine Therapy of Breat Cancer II*. Berlin, Heidelberg, Springer, 1987, 11–19.
11. Kaufmann M, Jonat W, Abel U. Adjuvant chemo- and endocrine therapy alone or in combination in premenopausal patients (GABG Trial 1). In Senn HJ, Goldhirsch A, Gelber RD, Osterwalther B, eds. *Recent Results in Cancer Research—Adjuvant Therapy of Primary Breast Cancer*. Berlin, Springer, 1989, 118–125.
12. Nomura Y, Tashiro H, Hisamatsu K, Shinozuka K. A randomized trial of adjuvant endocrine therapy, chemotherapy and chemoendocrine therapy for operable breast cancer stratified by estrogen receptor. *Cancer* 1988, **61**, 2168–2175.
13. Rose C, Mouridsen HT. Endocrine therapy of advanced breast cancer. *Acta Oncol* 1988, **27**, 721–728.
14. Mouridsen HT. Systemic therapy of advanced breat cancer. *Drugs* 1992, in press.
15. Kvinnsland S. Alternating sequences of tamoxifen and medroxyprogesteroneacetate in postmenopausal women with advanced breast cancer. *Proc Symp on MPA in Malignant Tumors*. Copenhagen, September 9, 1986. Abstract.
16. Kim U, Depowski M. Progression from hormone dependence to autonomy in mammary tumours as an *in vivo* manifestation of sequential clonal selection. *Cancer Res* 1975, **35**, 2068–2077.
17. Noble R. Hormonal control of growth and progression in tumors of Nb rats and a theory of action. *Cancer Res* 1977, **37**, 82–94.
18. Sluyser M, van Nier R. Estrogen receptor content and hormone responsive growth of mouse mammary tumors. *Cancer Res* 1974, **34**, 3253–3257.
19. Bruchowsky N, Rennie P, van Doorn E. Pathological growth of androgen sensitive tissue resulting from latent actions of steroid hormones. *J Toxicol Environ Health* 1978, **4**, 391–408.
20. Beex LVAM, Rose C, Sylvester R, Mignolet F. Continuous tamoxifen versus intermittent tamoxifen versus alternating tamoxifen and

medroxyprogesterone acetate. First line endocrine therapy for postmenopausal women with advanced breast cancer. A phase III study. *V EORTC Breast Cancer Working Conference*. Leuwen, 3–6 September 1991. Abstract A 324.
21. Fisher B, Redmond C, Wichkerham DL, *et al.* Doxorubicin containing regimens for the treatment of stage II breast cancer; The National Surgical Breast and Bowel Project Experience. *J Clin Oncol* 1989, 7, 572–582.
22. Mathe G, Plagne R, Morice V. Consistencies and variations of observations during serial analyses of a trial of adjuvant chemotherapy in breast cancer. In Salmon SE, ed. *Adjuvant Chemotherapy for Cancer*. Orlando, Grune & Stratton, 1987, 271–280.
23. Moliterni A, Bonadonna G, Valagussa P, Ferrari L, Zambetti M. CMF plus or minus adriamycin in the adjuvant treatment of breast cancer with 1–3 positive nodes. *Proc Am Soc Clin Oncol* 1990, 9, 19.
24. Wickerham D, Fisher B, Brown A, *et al.* Two months of adriamycin–cyclophosphamide (AC) with and without interval reinduction therapy vs. 6 months of conventional CMF in positive-node breast cancer patients non-responsive to tamoxifen; results of NSABP-15. *Proc Am Soc Clin Oncol* 1990, 9, 20.
25. Hryniuk W, Levine MN. Analyses of dose intensity for adjuvant chemotherapy trials in stage II breast cancer. *J Clin Oncol* 1986, 4, 1162–1170.
26. Henerson IC, Hayes DF, Gelman R. Dose-response in the treatment of breast cancer. A critical review. *J Clin Oncol* 1988, 6, 1501–1505.
27. International Breast Cancer Study Group. Late effects of adjuvant oophorectomy and chemotherapy upon breast cancer patients. *Ann Oncol* 1990, 1, 30–35.
28. Ragaz J, Jackson S, Wilson K, Plenderleith IH, Knowling M, Basco V. Randomized study of loco-regional radiotherapy (XRT) and ovarian ablation (OOPH) in premenopausal patients with breast cancer treated with adjuvant chemotherapy (CT). *Proc Am Soc Clin Oncol* 1988, 7, 12.
29. Everson LK, Ingle JN, Wieand HS, Martin JK, Votava RG, Fitzgibbons LH. Randomized trial of adjuvant therapy with cyclophosphamide, 5-fluorouracil, prednisone with or without tamoxifen following mastectomy in premenopausal patients with node-positive breast cancer. *Proc Am Soc Clin Oncol* 1986, 5, 63.
30. Fisher B, Redmond C, Brown A, *et al.* Adjuvant chemotherapy with and without tamoxifen: five-year results from the National Surgical Adjuvant Breast and Bowel Project Trial. *J Clin Oncol* 1986, 4, 459–471.
31. Tormey DC, Gray R, Taylor SG, Knuiman M, Olson JE, Cummings FJ. Postoperative chemotherapy and chemohormonal therapy in women with node positive breast cancer. *Natl Cancer Inst Monograph* 1986, 1, 75–81.
32. Dombernowsky P, Brincker H, Hansen M, Mouridsen HT, Overgaard M, Panduro J, *et al.* Adjuvant therapy of premenopausal and menopausal high-risk breast cancer patients. *Acta Oncol* 1988, 27, 691–697.
33. CRC Adjuvant Breast Trial Working Party. Cyclophosphamide and tamoxifen as adjuvant therapies in the management of breast cancer. *Br J Cancer* 1988, 57, 604–607.
34. Mouridsen HT, Ross C, Overgaard M, *et al.* Adjuvant treatment of postmenopausal patients with high risk primary breast cancer. *Acta Oncol* 1988, 27, 699–705.
35. Boccardo F, Rubagotti A, Bruzzi P, *et al.* Chemotherapy versus tamoxifen versus chemotherapy plus tamoxifen in node-positive estrogen receptor-positive breast cancer patients. Results of a multicentric Italian Study. *J Clin Oncol* 1990, 8, 1310–1320.
36. Goldhirsch A, Gelber RD. Adjuvant chemo-endocrine therapy or endocrine therapy alone for postmenopausal patients: Ludwig Studies III and IV. In Senn HJ, Goldhirsch A, Gelber RD, Osterwalder B, eds. *Recent Results in Cancer Research—Adjuvant Therapy of Primary Breast Cancer*. Berlin, Springer, 1989, 153–162.
37. Pearson OH, Hubay CA, Gordon NH, *et al.* Endocrine versus endocrine plus five-drug chemotherapy in postmenopausal patients wth stage II estrogen receptor-positive breast cancer. *Cancer* 1989, 64, 1819–1823.
38. Fisher B, Redmond C, Legault-Poisson S, *et al.* Postoperative chemotherapy and tamoxifen compared with tamoxifen alone in the treatment of positive-node breast cancer patients aged 50 years or older with tumours responsive to tamoxifen. Recent results of the national breast cancer and bowel project B 16. *J Clin Oncol* 1990, 8, 1005–1018.
39. Rivkin S, Green S, Metch B, Cruz A, McDivitt R, Knight W. Adjuvant combination chemotherapy (CMFVP) vs. tamoxifen (TAM) vs. CMFVP + TAM for postmenopausal women with ER+ operable breast cancer and positive axillary lymph nodes: An intergroup study. *Proc Am Soc Clin Oncol* 1990, 9, 24.
40. Axelsson CK, Mouridsen HT, Zedeler K. The node-negative breast cancer patient. *Eur J Cancer Clin Oncol* 1992, in press.

Eur J Cancer, Vol. 29A, No. 4, pp. 598–604, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00

Breast Cancer: Chemotherapy in the Treatment of Advanced Disease

M. Clavel and G. Catimel

Chemotherapy in patients with advanced breast cancer remains palliative. Although the majority of patients will experience an initial response or stabilisation of the disease, the survival is only modestly improved. The search for new drugs and more effective combinations must therefore continue. High-dose chemotherapy with or without autologous bone marrow transplant (ABMT) is an enthusiastic perspective of progress but the available data do not permit conclusions about the effectiveness of high-dose therapy compared with conventional treatment.
Eur J Cancer, Vol. 29A, No. 4, pp. 598–604, 1993.

INTRODUCTION

ALTHOUGH METASTATIC breast cancer is considered to be sensitive to chemotherapy, it remains incurable with current therapeutic approaches. Chemotherapy is usually reserved for endocrine-resistant patients, oestrogen receptor-negative patients, or patients who have life-threatening metastases. Various chemotherapeutic agents produce objective tumour responses.

Doxorubicin is the most effective single cytotoxic agent, giving a 40% response rate in previously untreated patients [1]. Combination chemotherapy regimens generally produce higher