Pergamon

European Journal of Cancer, Vol. 35, No. 12, pp. 1625–1627, 1999

Printed in Great Britain
0959-8049/99/$ - see front matter

PII: S0959-8049(99)00204-X

Editorial

Tamoxifen Added to Adjuvant Chemotherapy in Premenopausal Women with Early Breast Cancer: is it Standard Practice or Still a Subject for Study?

V.H.C. Bramwell[1] and K.I. Pritchard[2]

[1]London Regional Cancer Centre, London; and [2]Toronto Sunnybrook Regional Cancer Centre, 2075 Bayview Avenue, Toronto, Ontario, Canada M4N 3M5

OVER THE past 25 years, adjuvant systemic therapies, both endocrine and chemotherapy, have become an established part of the management of a majority of women with early stage breast cancer. Although the benefit of these treatments was first demonstrated in patients with high-risk node-positive disease [1, 2] subsequent clinical research has demonstrated similar reductions of relapse rates and mortality over a spectrum of baseline risks [3, 4]. Only those estimated to be at very low risk of recurrence (<10% at 10 years) of recurrence—typically women with small, node-negative tumours of low proliferative potential—are not routinely offered systemic therapy [5]. Early studies focused on the use of chemotherapy or hormone therapy as single modalities, which usually were selected on the basis of menopausal status and/or hormone receptor status. However, as each therapy benefited only a specific group of patients, combining these modalities in an attempt to overcome drug resistance provided an interesting rationale for a further generation of trials involving pre- and postmenopausal women.

In 1998, Colleoni and colleagues [6] published a systematic review of completed clinical trials comparing combined modality chemo-endocrine therapy with either of its component modalities alone. Its provocative title was: ''Combined chemo-endocrine adjuvant therapy for patients with operable breast cancer: still a question?'' In this editorial, we focus on their conclusions regarding the addition of endocrine therapy to chemotherapy in premenopausal patients, and we evaluate whether subsequent publications, including the Danish Breast Cancer Cooperative Group (DBCG) trial reported by Andersson and colleagues [7] in this issue of the *European Journal of Cancer,* have answered this question.

Colleoni and colleagues [6] identified 18 randomised trials which included 8965 patients, assessing whether tamoxifen (or in one trial medroxyprogesterone acetate) plus chemotherapy compared with chemotherapy alone improved relapse-free survival (RFS). Overall, 13 trials showed no evidence of benefit and five demonstrated an advantage for combined therapy. Where benefit was identified, it was generally seen in trials including postmenopausal patients, and often in studies in which tamoxifen was given in conjunction with anthracycline-based chemotherapy regimens. For premenopausal patients Colleoni and colleagues concluded ''there is little, although increasing, evidence that chemo-endocrine therapy is superior to chemotherapy alone''. To what extent do subsequent publications confirm or change this conclusion?

The update on the Oxford meta-analysis of tamoxifen trials, published in May 1998 by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), provided solid data on hormone treatment for many categories of women with early breast cancer, and showed that the benefits of adjuvant tamoxifen increased with duration of therapy [3]. For this analysis, information was available from 55 randomised trials, starting accrual before 1990. For 30 000 women with oestrogen receptor-positive (ER+) ($n = 18\,000$) or ER-unknown tumours randomised to tamoxifen versus no systemic therapy or to tamoxifen plus chemotherapy versus the same chemotherapy alone, the proportional reductions in recurrence at 10 years for patients receiving respectively 1 year, 2 years and 5 years of tamoxifen were 21% [±3], 29% [±2] and 47% [±3] with a highly significant trend towards greater effect for longer treatment ($2P < 0.00001$, two-tailed P value). The corresponding proportional mortality reductions were 12% [±3], 17% [±3] and 26% [±4], again with a significant test for trend ($2P = 0.003$). In contrast, the benefit experienced by women with ER-poor tumours ($n = 8000$) was small, although statistically significant, with a proportional reduction in recurrence of 10% [±4; $2P = 0.007$] and the benefit did not vary with duration of therapy.

The Oxford meta-analysis provided some information on the interaction of chemotherapy and endocrine therapy, although the authors caution that ''even such a large data-set cannot reliably support such excessively fine subdivision of the available evidence'' [3]. For postmenopausal women (defined as ≥50 years of age) with ER+/ER-unknown tumours, 5 years of tamoxifen in addition to chemotherapy was associated with a 54% [±8] reduction in recurrence rate and a 49% [±10] reduction in mortality. In contrast, the corresponding figures for the premenopausal age group (aged

Correspondence to K.I. Pritchard, e-mail: kathy.pritchard@tsrcc.on.ca
Received and accepted 4 Aug. 1999.

<50 years) were 40% [±19] and 39% [±22]. Too much confidence should not be placed in these latter findings because of the large standard deviations in this subgroup. Indeed, a detailed examination of the data reveals that only 205 women (28 of whom (14%) had ER-poor disease) aged <50 years were randomised into trials of 5 years of tamoxifen plus some months of concurrent chemotherapy versus the same chemotherapy alone (R. Peto, Clinical Trial Service Unit, Radcliffe Infirmary, Oxford, U.K.). Thus, there is an urgent unmet need for further evidence on the issue of chemo-endocrine treatment in premenopausal women.

The results of the DBCG trial [7] raise doubts about the benefits of concurrent chemotherapy and tamoxifen in premenopausal women. Following modified radical mastectomy, pre- and perimenopausal women (amenorrhoea for <5 years) with stage II or III breast cancer received CMF chemotherapy (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, 5-fluorouracil 600 mg/m^2 intravenously (i.v.) every 4 weeks, nine cycles) and then were randomised to receive no additional treatment ($n=314$) or concurrent tamoxifen 30 mg daily for 1 year ($n=320$). Forty per cent of participants had positive, 12% negative, and 48% unknown receptor status. With a median follow-up of 12.2 years there were absolutely no differences in RFS (10 years: 34% versus 35%, $P=0.81$) or in overall survival (45% versus 46%, $P=0.73$).

As acknowledged by the authors, certain features of this study, which started accrual in 1982, make it a less than ideal test of the concept of chemo-endocrine adjuvant therapy in premenopausal women. Chief among these is the short duration of tamoxifen therapy (1 year) and the limited number of women (40%) known to have ER+ tumours. The results of the EBCTCG meta-analysis, though, suggest that groups of patients with ER-unknown and ER+ tumours have similar outcomes on tamoxifen therapy. There is also the theoretical concern that tamoxifen given concurrently with chemotherapy could decrease the rates of cell division by allowing cells to enter G0, thus reducing their susceptibility to cell-cycle active chemotherapeutic agents [8]. Moreover, Goldenberg and colleagues [9] showed antagonism of cytocidal activity and uptake of melphalan by tamoxifen in human breast cancer cells *in vitro*. The hypothesis that it may be advantageous to give tamoxifen sequentially rather than concurrently with CAF (cyclophosphamide, doxorubicin, 5-fluorouracil) chemotherapy, was tested in postmenopausal women in Intergroup study 0100 [10], but data on this question are not yet available. In fact, concurrent administration of tamoxifen with anthracycline-based chemotherapy may not be an issue because tamoxifen can inhibit multidrug resistance [11] and has been demonstrated to have an additive effect with doxorubicin and cyclophosphamide *in vitro* [12].

Preliminary information from another trial, Intergroup study 0101 [13], supports the use of anthracycline-based chemo-endocrine therapy in premenopausal women with node-positive, receptor-positive breast cancer. In this three-arm trial, which recruited 1504 eligible patients, CAF alone was compared with CAF + goserelin (CAF + Z) and CAF + goserelin + tamoxifen for 5 years (CAF + ZT). Respective 5-year RFS figures were 67, 70 and 78%, and corresponding overall survival figures were 85, 86 and 86%. Only the difference in RFS between CAF and CAF + ZT was statistically significant ($P<0.01$). It should be noted that a combination of CAF + tamoxifen alone was not evaluated in this study.

The interaction of chemotherapy and tamoxifen may be complex in pre/perimenopausal patients. Amenorrhea frequently occurs in premenopausal patients who receive adjuvant chemotherapy, particularly with regimens containing alkylating agents, and has been associated with improved outcome [14]. More than 70% of patients receiving CMF in the Milan trial [2] stopped menstruating, and this was frequently permanent (95%) in women >40 years of age. It has been suggested that the major activity of chemotherapy is through a hormonal mechanism, but this issue remains controversial [15, 16]. When tamoxifen and chemotherapy are given concurrently to premenopausal women, before the menses stop, oestrone (E1) and oestradiol (E2) levels rise to 1–3× normal, while follicle stimulating hormone/luteinising hormone (FSH/LH) levels are unchanged. As the menses cease, FSH/LH levels rise whilst E1/E2 levels fall [17]. One scenario is that the efficacy of tamoxifen may vary depending on the hormonal milieu prevailing in the individual at the time of treatment, and that this may be variable and unstable across a group of pre/perimenopausal women.

Adjuvant chemotherapy is commonly recommended for premenopausal women with node-positive breast cancer, or with node-negative disease considered to have high-risk features. Should all these patients, or only those who have ER+ tumours, or none of them, routinely receive adjuvant tamoxifen? If tamoxifen is given, should treatment be concurrent or sequential? Should this decision depend on the type of chemotherapy?

There are several recently completed and ongoing studies that address these questions. A component of NSABP-B23 may provide some information for node-negative women with ER− tumours. This four-arm study, which completed accrual of 2000 pre- and postmenopausal patients in December 1998, compares CMF (oral) + placebo versus CMF + tamoxifen for 5 years, versus AC (doxorubicin, cyclophosphamide) + placebo versus AC + tamoxifen for 5 years. The International Breast Cancer Study Group protocol IBCSG-13-93 is scheduled to complete accrual of 1225 premenopausal node-positive patients in mid-1999. Its primary question evaluates the importance of a 16 week gap between AC and CMF (oral) chemotherapy. A second randomisation, however, investigates the value of 5 years of tamoxifen starting at the end of chemotherapy. ER status must be known, but can be positive or negative. A Scottish study, SCTN-BR9403, including pre- and postmenopausal patients, evaluates the benefits of 5 years of tamoxifen starting after completion of six cycles of CMF (i.v.). EORTC 10901 has a similar design, but permits a wider range of chemotherapies (CMF×6, 5-fluorouracil, doxorubicin, cyclophosphamide; FAC×6, 5-fluorouracil, epirubicin, cyclophosphamide; FEC×6, CAF×6, cyclophosphamide, epirubicin, 5-fluorouracil; CEF×6) followed by 3 years of tamoxifen treatment. The SCTN and EORTC studies closed to accrual in early 1999, between them recruiting 1800 patients, and the data will be combined for analysis.

A Canadian study, NCIC MA-12, includes pre/perimenopausal patients with node-positive and high-risk node-negative (high grade, and/or lymphovascular invasion) breast cancer. ER status must be known, but can be positive or negative. After six cycles of CMF (oral) or CEF [18], or four cycles of AC [19] patients are randomised to 5 years of tamoxifen versus placebo. Projected accrual is 800 patients, and this study should be completed within the next 1–2 years.

Based on the evidence thus far, the trend towards increasing use of chemo-endocrine therapy in many categories of women with early breast cancer is appropriate. We would argue, however, for caution in the additional use of tamoxifen in premenopausal women who are felt to be at sufficient risk of relapse to require adjuvant chemotherapy. Recently completed or current trials should provide definitive evidence as to any additional benefit derived by adding 5 years of tamoxifen to chemotherapy in premenopausal patients with ER+ tumours, and whether this benefit extends to patients with ER− tumours. These studies might also tell us whether tamoxifen should be delayed until the end of chemotherapy, and should help to determine the optimal chemotherapy regimen (i.e., CMF or anthracycline-based) to be used in conjunction with tamoxifen. We await the outcome of these various trials with great interest.

1. Fisher B, Fisher ER, Redmond C, *et al*. Ten year results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trial evaluating the use of L-Phenylalanine Mustard (L-PAM) in the management of primary breast cancer. *J Clin Oncol* 1986, **4**, 929–941.
2. Bonadonna C, Brusamolino E, Valagussa A, *et al*. Combination chemotherapy as an adjuvant treatment in operable breast cancer. *N Engl J Med* 1976, **294P**, 405–410.
3. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomized trials. *Lancet* 1998, **351**, 1451–1567.
4. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomized trials. *Lancet* 1998, **352**, 930–942.
5. Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. 7. Adjuvant systemic therapy for women with node-negative breast cancer. *Can Med Assoc J* 1998, **158**(Suppl. 3), S43–S51.
6. Colleoni M, Coates A, Pagani O, Goldhirsch A. Combined chemo-endocrine adjuvant therapy for patients with operable breast cancer: still a question? *Cancer Treat Rev* 1998, **24**, 15–26.
7. Danish Breast Cancer Cooperative Group. Tamoxifen in high-risk premenopausal women with primary breast cancer receiving adjuvant chemotherapy. *Eur J Cancer*, this issue.
8. Osborne CK. Effects of estrogen and antiestrogens on cell proliferation. Implications for treatment of breast cancer. In Osborne CK, ed. *Endocrine Treatment in Breast and Prostate Cancer*. Boston, Kluwer, 1988, 11–129.
9. Goldenberg GJ, Froese EK. Antagonism of the cytocidal activity and uptake of melphalan by tamoxifen in human breast cancer cells *in vitro*. *Biochem Pharmacol* 1985, **34**, 763–770.
10. Albain K, Green S, Osborne K, *et al*. Tamoxifen (T) versus cyclophosphamide, adriamycin and 5-FU plus either concurrent or sequential T in postmenopausal, receptor (+), node (+) breast cancer: a Southwest Oncology Group phase III intergroup trial (SWOG-8814, INT-0100). *Proc Am Soc Clin Oncol* 1997, **16**, 128a.
11. Foster BJ, Crotzinger KR, McKay WM, *et al*. Modulation of induced resistance to adriamycin in two human breast cancer cell lines with tamoxifen or perhexiline maleate. *Cancer Chemother Pharmacol* 1988, **22**, 147–152.
12. Smith C, Henderson JC. New treatments for breast cancer. *Semin Oncol* 1996, **23**, 506–508.
13. Davidson N, O'Neill A, Vukov CK, *et al*. Effect of chemohormonal therapy in premenopausal node (+), receptor (+) breast cancer: an Eastern Cooperative Oncology Group phase III Intergroup trial (E5188, INT-0101). *Proc Am Soc Clin Oncol* 1999, **18**, 67a.
14. Pagani O, O'Neill A, Castiglione M, *et al*. Prognostic impact of amenorrhea after adjuvant chemotherapy in premenopausal breast cancer patients with axillary node involvement: results of the International Breast Cancer Study Group (IBCSG) trial VI. *Eur J Cancer* 1998, **34**, 632–640.
15. Powles TJ. Prognostic impact of amenorrhea after adjuvant chemotherapy. *Eur J Cancer* 1998, **34**, 603–605.
16. Jordan VC. Chemotherapy is antihormonal therapy—how much proof do oncologists need? *Eur J Cancer* 1998, **34**, 606–608.
17. Delrio G, De Placido S, Pagliarulo C, *et al*. Hypothalamic–pituitary–ovarian axis in women with operable breast cancer treated with adjuvant CMF and tamoxifen. *Tumori* 1986, **72**, 53–61.
18. Levine MN, Bramwell VH, Pritchard KI, *et al*. Randomized trial of intensive cyclophosphamide, epirubicin and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer. *J Clin Oncol* 1998, **16**, 2651–2658.
19. Fisher B, Brown AM, Dimitrov NV, *et al*. Two months of doxorubicin–cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumours: results from the National Surgical Adjuvant Breast and Bowel Project B-15. *J Clin Oncol* 1990, **8**, 1483–1496.