

Table: Breast Cancer Events (Tamoxifen vs Placebo)

|   | Marsden <sup>7</sup> | Italian <sup>7</sup>            | NSABP P-1 <sup>3</sup> | IBIS-1             |
|---|----------------------|---------------------------------|------------------------|--------------------|
| Total n                                       | 2471                 | 5408                            | 13,388                 | 7139               |
| Follow-up: woman-yrs x 10 <sup>3</sup>        | 12.2                 | 17.2                            | 26.2                   | 15.0               |
| Breast cancer (risk reduction)                | 5.0% vs 6.1% (18%)   | 1.3% vs 1.7% <sup>a</sup> (24%) | 1.9% vs 3.6% (49%)     | 1.9% vs 2.8% (32%) |
| ER-positive invasive disease (risk reduction) | 2.5% vs 3.6% (31%)   | 0.7% vs 1.1% <sup>a</sup> (36%) | 0.6% vs 1.9% (69%)     | 1.2% vs 1.8% (31%) |
| ER-negative invasive disease                  | 1.4% vs 0.8%         | 0.5% vs 0.4%                    | 0.6% vs 0.5%           | 0.5% vs 0.5%       |
| Non- invasive disease events incidence        | 0.6% vs 0.6%         | 0.2% vs 0.1%                    | 0.5% vs 1.0%           | 0.1% vs 0.4%       |

<sup>a</sup> includes non-invasive cancers

While the differences in the results of these studies have generated much discussion, there are two evident consistencies:

1. tamoxifen reduces the risk of ER-positive invasive breast cancer; a meta-analysis of the four studies shows a risk reduction of 48% in this group<sup>6</sup>
2. tamoxifen has no effect on the risk of ER-negative invasive breast cancer; differences in efficacy between the studies are most likely explained by differences in study populations in terms of breast cancer risk and concurrent use of HRT.

The adverse effects reported in IBIS-1 are consistent with those seen in previous chemoprevention and adjuvant tamoxifen studies. In the prevention setting, tamoxifen is associated with an excess of endometrial cancer (RR=2.4), and venous TE events (RR=1.9). The absolute risk of TE events increases with age, but the relative increase in risk from tamoxifen appears to be constant. Interestingly, there is a numerical, although not significant, excess of new colorectal cancer cases in two of the prevention studies (IBIS-1 and NSABP P-1).

An unexpected finding of the Women's Health Initiative study was that HRT

significantly reduces the incidence of colorectal cancer.<sup>8</sup> As the prevention studies mature, it will be interesting to follow the incidence of colorectal cancer. The higher mortality seen in the tamoxifen group of the IBIS-1 trial was unexpected. This may be a chance finding, however, as deaths were from a range of causes that were not attributable directly to tamoxifen. In the meta-analysis of all four studies, no effect on all-cause mortality was seen. Prevention strategies will necessarily treat many women who will not develop breast cancer. Current data suggest that, despite a risk reduction of 48%, only 1% of women who start tamoxifen as a preventative strategy will avoid an invasive breast tumour. The 5-year incidence of breast cancer is low (2–6%), even in the high-risk populations chosen for these prevention studies. Furthermore, tamoxifen is associated with hot flushes and vaginal symptoms in the majority of women, and with potentially lethal TE events and endometrial cancer in a few. It is noteworthy that compliance to 5 years was generally poor in the prevention studies.

In summary, the role of tamoxifen in the prevention setting remains unclear and therefore should not be recommended for use as breast cancer prevention outside a clinical trial. Although tamoxifen does reduce the incidence of ER-positive breast

cancer, it has not been shown to be associated with a survival benefit, and it may be associated with an adverse effect on mortality. Further follow-up of these studies is required. Hormonal agents with different safety profiles need to be pursued: raloxifene and anastrozole are the subjects of the next generation of breast cancer prevention studies (NSABP P-2 and IBIS-2, respectively). Finally, markers that can differentiate risk of ER-positive disease from risk of ER-negative disease need to be identified so that different prevention strategies can be developed for these two distinct clinical entities.

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# CLINICAL UPDATE

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## Dose-dense chemotherapy as adjuvant treatment in early breast cancer

By Dr Anna Nowak, Medical Oncologist, NHMRC Clinical Trials Centre, University of Sydney, NSW.

Citron ML, Berry DA, Cirincione C *et al*. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of intergroup trial C9741/Cancer and Leukemia Group B Trial 9741. *Journal of Clinical Oncology* 2003;21:1431–1439.

#### Objective

To investigate the role of dose density and of sequential versus concurrent chemotherapy in the adjuvant treatment of node-positive early breast cancer (EBC).

#### Study design

This prospective, randomized, 2 x 2 factorial design trial randomised women with T0–3, N1/2, M0 EBC to one of four arms within 84 days of primary surgery. All arms received the same dose of each drug per cycle and the same total dose of each drug: doxorubicin (A) 60mg/m<sup>2</sup>/cycle; paclitaxel (T) 175 mg/m<sup>2</sup>/cycle; and cyclophosphamide (C) 600mg/m<sup>2</sup>/cycle. From September 1997–March 1999, 2005 women were randomised to receive one of the following:

- A x 4 doses, followed by T x 4 doses, followed by C x 4 doses: with doses either every 3 weeks without filgrastim (n=484), or every 2 weeks with filgrastim (n=493)
- concurrent AC x 4 doses, followed by T x 4 doses: with doses either every 3 weeks without filgrastim (n=501), or every 2 weeks with filgrastim (n=495).

Tamoxifen 20mg/day was recommended for all post-menopausal women and for pre-menopausal women with hormone receptor-positive cancers, starting after completion of chemotherapy and continuing for 5 years. The primary endpoint was disease free survival (DFS). Secondary endpoints were overall survival (OS) and toxicity.

#### Results

1973 women received protocol treatment and were included in the analysis. After a median follow-up of 36 months, DFS was significantly prolonged in the dose-dense therapy arms of the trial, compared with the 3-weekly arms (risk ratio 0.74, p=0.01, 3-year DFS 85% vs 81%), with the effect remaining statistically significant after adjustment for number of positive nodes, tumour size, menopausal status and oestrogen receptor (ER) status. DFS did not correlate with treatment sequence, and no interaction between dose density and treatment sequence was found. OS was significantly prolonged in the dose-dense arms (risk ratio = 0.69, p=0.013, 3-year OS 92% vs 90%), but was not affected by treatment sequence and there was no interaction between dose density and sequence of treatment. Patterns of the site of first recurrence were similar in all trial arms.

Detailed toxicity data are available for 412 patients over 3973 treatment cycles. More dose delays due to haematological toxicity occurred in the 3-weekly than the 2-weekly arms (p<0.0001). Grade 4 granulocytopenia (< 500/μl) was more common in the 3-weekly arms compared with the 2-weekly arms (33% vs 6%, p<0.0001). However 13% of women in the concurrent dose-dense arm needed a red blood cell transfusion. Late toxicities (cardiomyopathy, myelodysplastic syndrome (MDS) and acute myelogenous leukaemia (AML)) did not show any clear pattern amongst the four arms. Severe chemotherapy-related neurotoxicity was rare but more frequent in the concurrent arms than the sequential arms (4% vs 2%, p=0.005).

#### Conclusion

Dose-dense chemotherapy, as delivered in this study, improves DFS and OS compared with conventional regimens. These advantages are not accompanied by an increase in toxicity. Sequential chemotherapy is as effective as concurrent chemotherapy.

#### COMMENTARY

The concept of dose-dense chemotherapy has intrigued oncologists since Skipper proposed his model of log cell kill, in which chemotherapy kills a constant fraction of growing cancer cells rather than a constant number.<sup>1</sup> This concept was refined by Norton and Simon, who predicted that administering chemotherapy more frequently, in a dose-dense manner, could decrease tumour regrowth between cycles.<sup>2,3</sup>

Adjuvant chemotherapy for EBC has been a major testing ground for these concepts. Five therapeutic models of dose intensification, discussed below, have been proposed.<sup>4</sup> Possible variables include total dose per cycle, total cumulative dose, and interval between cycles. Many of these studies attempting to address questions of dose intensification have been confounded by differences in dose per cycle and total dose of drugs other than those under study, or differences in the drug combination in each arm.

Three models of dose intensification use increasing doses per cycle with the same cycle duration, and increased, decreased or maintained cumulative drug doses, respectively. Fisher *et al*. published the only trial examining dose intensification of cyclophosphamide in adjuvant chemotherapy for EBC, showing no benefit to DFS or OS for increasing either the dose per cycle while maintaining cumulative dose and dosing interval, or increasing both the dose per cycle and the cumulative dose.<sup>5</sup> There have, however, been numerous trials of dose intensification of anthracyclines. Increasing the doxorubicin dose per cycle, while maintaining the cumulative dose and dose interval, has not been found to improve OS.<sup>6</sup> Similarly, there is no evidence of a doxorubicin dose effect at three increasing dose levels and cumulative doses while cycle length is maintained.<sup>7</sup> Trials of epirubicin dose intensification have produced conflicting results. Two trials demonstrated survival benefits from increasing the epirubicin dose per cycle and cumulative dose without changing the cycle duration,<sup>8,9</sup> whilst a third did not.<sup>10</sup> The third study also

indicated superior DFS, but not OS, for a decreased dose per cycle but increased cumulative dose and number of cycles of epirubicin, while maintaining a constant cycle interval.<sup>10</sup>

A fourth model of dose intensification proposes both a decreased dose per cycle and dosing interval, as is used in weekly chemotherapy schedules. There are as yet no mature phase III trials testing this strategy in EBC.

Citron *et al.* examined a fifth model of dose intensification, involving a constant dose per cycle and cumulative drug dose, but a shortened dosing interval. This model has been examined in adjuvant treatment of EBC by only one other published trial,<sup>11</sup> which found no survival advantage for dose-dense epirubicin. However, the trial was confounded by the inclusion of 5-fluorouracil in one arm, differing routes of cyclophosphamide administration and splitting the epirubicin dose in one arm.

The study by Citron *et al.* described above examined the role of dose density separately from total dose and number of cycles, whilst simultaneously examining the role of sequential versus combination chemotherapy in a 2 x 2 factorial design. There were no major confounding factors: identical drugs and doses were given with each cycle, and the total dose was the same in each arm. The study arms differed, necessarily, in their use of filgrastim (recombinant human granulocyte colony stimulating factor G-CSF), and total treatment duration ranged from 14 weeks (2-weekly AC → T) to 33 weeks (3-weekly A → T → C). The study was adequately powered to detect a 33% difference in hazard ratio for either DFS or OS, and patient numbers were increased appropriately to accommodate rapid accrual. Although the study was not analysed by intention-to-treat, fewer than 2% of patients were excluded from the analysis because they did not receive chemotherapy, a proportion which is unlikely to alter the results.

The trial demonstrated a significant risk ratio reduction for both DFS (risk ratio 0.74, p=0.01) and OS (risk ratio 0.69, p=0.013) with dose-dense, compared with conventionally scheduled, chemotherapy. However, relatively few events had occurred, with 315 relapses or deaths (15%) at a median follow-up of 36 months, compared with 515 expected treatment failures (based on the event rate observed in CALGB 8541).<sup>12</sup> The absolute differences in OS between the dose-dense and conventional dosing arms were relatively small (92% versus 90% at 3 years). Thus, although the trial found a benefit for dose-dense chemotherapy, the median follow-up is too short to give mature data from an adjuvant trial, and the

risk ratios may change with longer follow-up and more events. The toxicity profiles of the dose-dense regimens were acceptable, with lower rates of grade IV granulocytopenia in these arms due to the mandatory use of filgrastim, and low rates of febrile neutropenia in all arms. However, blood transfusion was needed for 13% of patients in the AC → T 2-weekly arm. Filgrastim use did not increase the incidence of MDS or AML, but follow-up remains short and the number of patients for whom toxicity data are available is small. It is unclear why detailed toxicity data was not collected on all patients. Crump *et al.* found that the median time to developing anthracycline-related leukaemia was 18 months after completing adjuvant chemotherapy, with a range of 14–79 months.<sup>13</sup> Thus, longer follow-up and long-term toxicity data for larger patient numbers will be needed before firm conclusions can be drawn.

Citron *et al.* did not include any economic analysis in this trial. The use of filgrastim adds to the treatment cost and the burden of treatment for patients. The burden of daily injections may be reduced by using pegfilgrastim, although there are no data on pegfilgrastim in this setting. Implementation of these data in Australia will be limited by the current PBS listing for G-CSF. It would be interesting to evaluate the relative costs of filgrastim versus the economic benefits of shorter treatment duration. The other noticeable absence in this trial is any quality of life evaluation.

Should we be changing our practice on the basis of these results? Probably not yet. The follow-up of this trial is immature, the number of events seen is fewer than predicted,<sup>12</sup> and the absolute differences are currently small. Other large, well-designed trials confirming the benefits of dose-dense chemotherapy are needed before a change in practice can be justified. It is possible that some patients benefit more than others, and future trials must be appropriately stratified and adequately powered to examine any differential effects of dose-dense treatment on subgroups according to hormone receptor and HER-2 status. Clinicians should be encouraged to enrol appropriate patients into clinical trials testing dose-dense strategies.

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## Chemoprevention: is the jury still out?

By Dr Rohini Sharma, Medical Oncology Registrar, and Dr Anne Hamilton, Medical Oncologist, Royal Prince Alfred Hospital, Sydney, NSW.

International Breast Cancer Intervention Study investigators. First results from the International Breast Cancer Intervention Study (IBIS-1): a randomised prevention trial. *The Lancet* 2002;360:817–824.

### Objective

To assess the efficacy and tolerability of tamoxifen for primary prevention of breast cancer in women at high risk.

### Study design

An international double-blind placebo-controlled randomised trial. Eligible women had risk factors for breast cancer indicating at least a two-fold relative risk (RR) for ages 45–70 years, a four-fold RR for ages 40–44 years, and an approximately ten-fold RR for ages 35–39 years. Women were randomised to tamoxifen 20mg/day or matched placebo for 5 years. Participants had had a baseline mammogram within 12 months prior to starting the trial, and were followed-up every six months during the 5 years of active treatment. For up to 5 years after treatment completion, participants attended clinical visits or completed questionnaires annually. Mammography was repeated every 12–18 months.

### Outcome measures

The primary endpoint was incidence of breast cancer (including ductal carcinoma in situ). Subgroup analyses in patients developing tumours were oestrogen receptor (ER) status of the cancer, use of hormonal replacement therapy (HRT), and age (<50, ≥50 years). Secondary endpoints were incidence of other cancers, thromboembolic (TE) events, cardiovascular events and cause-specific mortality.

### Results

7152 women (37% from Australia and New Zealand) were recruited between April 1992 and March 2001. Of these, 7139 were included in the analysis after exclusion of 13 women who had not had their baseline mammogram until after recruitment and were found to have breast cancer at baseline. After a median follow-up of 50 months, 25% of women had completed 5 years of study treatment and 47% were still receiving treatment. Full treatment compliance was estimated at 64% and 74% in the tamoxifen and placebo groups, respectively. Forty percent of women took HRT during the treatment period. A total of 101 breast cancers (85

invasive) occurred in 3566 women receiving placebo, and 69 (64 invasive) occurred in 3573 women receiving tamoxifen (risk reduction 32%, p=0.013). Risk reduction for invasive and non-invasive disease was 25% and 69%, respectively. The difference found for invasive cancers was attributable to a reduction in ER-positive tumours (risk reduction 31%); there was no risk reduction for ER-negative invasive cancer. Age at randomisation, degree of risk and use of HRT did not affect the risk reduction. Two patients in each arm died of breast cancer.

There was a non-significant excess of endometrial cancer in the tamoxifen group compared with placebo (11 vs 5, p=0.2). Most cases of endometrial cancer (n=13) occurred in women who were older than 50 years at randomisation and all of the women affected were post-menopausal. The majority of tumours were adenocarcinomas and most were of FIGO stage I. No deaths were attributed to endometrial cancer. Other cancers were equally distributed between the treatment arms (39 per treatment group). Women randomised to tamoxifen were more likely to develop a TE event than those in the placebo group (43 vs 17 events, risk increase of 2.5, p=0.001, excluding superficial thrombophlebitis). Five patients died of TE events with no difference between the two arms. Vasomotor and gynaecological symptoms were more common (82% vs 68%) and breast complaints were less common (15% vs 19%) in the tamoxifen group compared with placebo. Other side effects were distributed equally between the two groups.

The number of deaths from all causes was significantly higher in the tamoxifen group compared with placebo (25 vs 11, p=0.028). Deaths from cancer (12 vs 6) and cardiovascular causes (11 vs 4) were higher in the tamoxifen group. The excess in TE deaths in the tamoxifen group indicated that deaths from cardiovascular causes may be attributed to tamoxifen. The authors concluded that the excess of cancer deaths may be a chance finding, as the overall cancer incidence rates were similar in the two treatment arms, and a variety of primary tumours were represented.

### Conclusion

In a high-risk population, 5 years of tamoxifen reduces the risk of breast cancer events (including non-invasive events) by 32%, and the risk of ER-positive invasive breast cancer by 31%. This effect is accompanied by a doubling in the risk of endometrial cancer and a 2.5-fold increase

in TE events. Mortality was significantly higher in women randomised to tamoxifen; however a causative role for tamoxifen in the excess of cancer deaths not due to breast cancer has not been established. The overall risk-to-benefit ratio for tamoxifen in breast cancer prevention remains unclear.

## COMMENTARY

Breast cancer is the most common cause of cancer death in Australian women, and prevention strategies therefore have significant public health implications.<sup>1</sup> The IBIS-1 trial is one of four randomised placebo-controlled studies (NSABP P-1,<sup>2</sup> Italian,<sup>3</sup> Marsden,<sup>4</sup> IBIS-1) that have investigated the role of tamoxifen in the prevention setting. Differences in the designs and results of these studies have already been the subject of formal overviews,<sup>5,6</sup> as well as an elegant editorial.<sup>7</sup>

All of the studies, other than the Marsden trial, were multi-institutional and all used tamoxifen at a dose of 20mg/day. The Marsden trial allowed up to 8 years of therapy; all the others used 5 years. Each study enrolled women at high risk of developing invasive breast cancer, but each used its own definition of high risk. The IBIS-1 trial used an algorithm that incorporated the number of first- or second-degree relatives with a history of breast cancer, and the age at diagnosis, as well as personal factors including age, parity, and history of benign breast pathologies (lobular carcinoma in situ or atypical hyperplasia). Of the four trials, only NSABP P-1 prohibited the use of HRT.

NSABP P-1 is the largest study with over 13,000 participants, followed by IBIS-1 (n=7152). The Marsden study is the smallest (n=2471), and has the fewest woman-years of follow-up as a result, but it has the longest median follow-up and has recruited a younger population than the other studies (median age 47 years compared with 50 years or older for the other studies). At similar follow-up the incidence of breast cancer events in the placebo arm of the Marsden study was nearly twice that of NSABP P-1, suggesting that the Marsden study may include a greater proportion of women at high risk of developing breast cancer.

The IBIS-1 trial is still relatively immature, with 15.0 x 10<sup>3</sup> woman years of follow-up in each arm, a median follow-up of 50 months, and 47% of patients still receiving study treatment. However, the incidence of ER-positive invasive breast cancer in the placebo arm of IBIS-1 (1.8%) is comparable with first reports from other studies.