The recent publication of the NSABP-B35 trial provides important information about the relative value of anastrozole (ANA) over tamoxifen (TAM) for post-menopausal women with ductal carcinoma in situ (DCIS) treated with conservative surgery (CS) and radiotherapy (RT). However, the clinician is still left wondering when adjuvant hormonal treatment (HT) should be prescribed for the individual patient and now whether to use ANA instead of TAM (1).

Margolese et al. [2016] examined HT for post-menopausal women with estrogen receptor (ER)-positive DCIS using a double-blinded, phase 3 clinical trial after CS + RT. NSABP North American centres (n=333) from January 2003–June 2006 enrolled 3,104 women to TAM (20 mg daily) or ANA (1 mg daily). The primary endpoint was breast cancer-free interval (BCFI).

With a median follow-up of 9.0 years, and 64% compliance in both groups, a significant decrease was found in all [hazard ratio (HR) 0.73, P=0.0234] and invasive (HR 0.62, P=0.0123) BCFI events from ANA. More specifically, the significant reduction in BCFI events was only seen in total (HR 0.64, P=0.0322) and invasive (HR 0.52, P=0.0148) contralateral disease. All other recurrence ratios (DCIS or invasive disease) were not significant. Further, the authors could not explain why the benefit of ANA over TAM was only seen in post-menopausal women aged under 60 years of age (P=0.0379). For older women, TAM or ANA were equivalent; Forbes et al. have recently published on the IBIS-II DCIS trial with median follow-up of 7.2 years, where 2,980 post-menopausal women diagnosed with DCIS treated with CS (29%) or CS + RT (71%) were randomised to TAM or ANA for 5 years (2). No statistically significant differences in overall, ipsilateral, contralateral, invasive or non-invasive recurrence or proportional adverse effects were observed.

Of course the decision not to use HT is easy if a patient has a high-grade ER-negative DCIS. ER expression is very high in patients with low-to-intermediate grade DCIS (around 90%) compared with high-grade DCIS (about half) (3-5). Given the majority of patients do have ER-positive DCIS, the NSABP-B35 provides some new information to help us if we choose to recommend HT. Previous studies have documented the importance of RT after CS for DCIS although debate still goes on about its use in small low-grade lesions (6).

We have previously reported using a meta-regression technique to examine 9,404 DCIS cases with a minimum 10-year follow-up. The adjusted invasive ipsilateral local recurrence (ILR) rate in our review was statistically significantly lowered with the addition of TAM only in the setting of CS + RT: CS-alone, 11.3%; CS + RT, 7.2% and CS + RT + TAM, 4.7%, with no significance observed between CS-alone and CS + TAM, 11.0% (7). However, there was no difference in 10-year breast cancer-death rate. In the NSABP-B35 study, with shorter follow-up ILR was 1.4% for CS + RT + TAM vs 1.1% for CS + RT + ANA (P=NS).

It is puzzling to understand why TAM did not reduce the ILR rates in our long-term study in women treated with
CS-alone, and why TAM improved the invasive ILR rate in those with CS + RT. Cuzick et al. reported significant rate reductions with TAM for DCIS ILR (HR 0.71), and contralateral LR of invasive (HR 0.47) and DCIS (HR 0.36), but TAM had no effect on invasive ILR rates independent of RT delivery (HR 0.95) (8). Conversely, Wapnir et al. observed a significant 32% reduction in invasive ILR for patients treated with CS + RT when TAM was added (9).

We know clinically that elderly patients with invasive breast cancer treated with TAM rather than a mastectomy eventually progress due to tumour resistance to this cytostatic drug (10). Given the long follow-up in our meta-regression study, it is possible any residual tumour cells would have become resistant. On the other hand, the ILR rate was reduced when TAM was added to CS + RT. RT not only sterilizes residual cancer cells within the breast, but could additionally have a synergistic effect when combined with TAM.

In other words, the effect of TAM or ANA is small; close to 3,000 DCIS patients taking HT for 5 years to reduce the risk of a contralateral invasive breast cancer for at least 10,000 life years of treatment and appointments for probably no survival benefit at all. Although not significant, there was an increased number of uterine cancers observed in the TAM group (1.1% vs. 0.5%) and conversely, more osteoporotic fractures were seen in the ANA group (4.5% vs. 3.3%) (1).

The question then becomes “is the pain worth the gain” for adding a daily reminder with probable side-effects for patients who do not currently have invasive breast cancer. As clinicians, we must ‘first, do no harm’. Nomograms have provided some general guidance for treatment, and with testing providing some assurance (11,12). The usual decision-making for a clinician includes communicating the risk of a local recurrence with or without radiation, explaining that about half of the ILRs are DCIS and still curable. An explanation may also be given that a recurrence in the treated breast may involve a mastectomy and for some patients, chemotherapy. Trying to communicate the fact that an invasive recurrence can lead to increased mortality adds fear and confusion for the patient. The conversation can be complicated enough before the added dimension of explaining that HTs “may” help reduce recurrence but not necessarily improve survival rates. Many of us know, that it is often more difficult to consult with a patient with a diagnosis of DCIS than invasive breast cancer and many patients are left confused (13).

Ganz et al. reported in the NSABP-B35 companion paper on quality-of-life for 1,193 patients (14). Over 5 years, no significant difference was detected between the TAM and ANA groups for physical and mental health scores, energy and fatigue, symptoms of depression, sexual functioning. However, as to be expected, the TAM group had significantly more vasomotor symptoms (P=0.011), difficulty with bladder control (P=0.0002), and gynaecological symptoms (P<0.0001). Those in the ANA group had significantly more musculoskeletal pains (P=0.0006) and vaginal symptoms (P=0.035). In general, younger women (aged <60 years) had more severe vasomotor (P=0.0006), vaginal (P<0.0001), gynaecological (P=0.014) symptoms and weight problems (P<0.0001), than those aged ≥60 years.

At baseline, hot flushes were present in 29% of TAM and 26% of ANA patients increasing to 39% and 34% respectively by 6 months of adjuvant treatment. Pain with intercourse increased from 20% and 18% at baseline to 24% and 25% with TAM and ANA respectively. Muscle stiffness was 64% at baseline for both groups increasing to 68% and 78% for TAM and ANA respectively. In other words, the small gains in reduced contralateral tumour recurrence come at the expense of more pain.

But what about long-term? Margolose et al. found divergence in the curves after five years showing benefit for ANA for all and invasive BCFI events compared with TAM. Similarly, the ATAC invasive breast cancer data saw a small improvement with ANA versus TAM early on, which went on to become greater as years progressed (15).

The use of TAM or ANA in this setting could also be compared to the 5-year use of TAM in high-risk patients without breast cancer—the IBIS-1 study (16). After a median follow up of 16.0 years, 601 breast cancers were reported [251 (7.0%) in 3,579 patients in the TAM group versus 350 (9.8%) in 3,575 women in the placebo group]. The benefit of TAM was significantly greater in women who did not use menopausal hormone therapy during the treatment period than in those who used this therapy, indicating clear loss of efficacy of TAM when menopausal hormone therapy was used concomitantly. Despite the marked reduction in breast cancer events, TAM had no effect on breast cancer-specific mortality 31 deaths with TAM versus 26 with placebo. The same may be the case for patients with DCIS.

Why is there benefit of ANA only in younger postmenopausal women? The NSABP-B35 study commenced in 2003. In 2001, in California, for example, 52.4% of 55–59 years old were using hormone replacement therapy (HRT) (17). The scare from the results of the Women’s
Health Initiative was published in July 2002. It is likely that many women in this study had previously taken HRT the year before enrolment. There is at least some basic evidence that estrogen priming may improve the efficacy of an aromatase inhibitor (18) and reduce the efficacy of TAM (16). One can only speculate that perhaps TAM and ANA are as good as each other as shown in the older postmenopausal group.

ANA has provided a significant but small improvement in BCFI, mainly in post-menopausal women aged under 60 years old, and only in the opposite breast when compared with TAM. This NSABP-B35 study has provided the DCIS patient and prescribing clinician a choice of endocrine therapies; as always, the absolute benefit of treatment must be balanced with toxicity of treatment. Possible candidates for TAM or ANA are patients with DCIS with other risk factors for a second primary cancer such as a first-degree family history, particularly at a young age, the presence of dense breasts or surrounding pathology showing areas of lobular carcinoma in situ (LCIS) or severe atypical hyperplasia. For these patients, the pain may be worth the gain.

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Footnote

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Conflicts of Interest: John Boyages is author of DCIS of the Breast: Taking Control (www.bcpublish.com) and receives royalties. The other author has no conflicts of interest to declare.


References


