Institution: The University of Manchester

Unit of Assessment: 1

Title of case study:
Preventing bone loss in patients treated for breast cancer

1. Summary of the impact

Aromatase inhibitors (AIs) significantly improve survival from breast cancer but are associated with increases in osteoporotic fractures and bone mineral density loss. Research at the University of Manchester (UoM) has provided key evidence that has contributed to preventing debilitating bone demineralisation safely in breast cancer patients undergoing adjuvant therapy with AIs. UoM findings have led to an international consensus on guidelines recommending Dual-energy X-ray Absorptiometry (DEXA) scanning to identify patients at risk of bone loss as well as the use of bisphosphonates where bone loss has been identified. Further guidelines advise against the use of HRT to treat bone loss as a result of its association with breast cancer recurrence.

2. Underpinning research

See section 3 for references 1-6. UoM researchers are given in bold.

Background

Two large International trials, Arimidex Tamoxifen Adjuvant Combination (ATAC) (1) and the Breast International Group (BIG) 1-98 Study (*New England Journal of Medicine*, 353:2747-2757), confirmed the superiority of non-steroidal aromatase inhibitors (AIs) used for five years after surgery, compared with Tamoxifen, in preventing breast cancer recurrence. The findings led to the widespread use of AIs internationally and AIs are now the standard NICE approved treatment for breast cancer in oestrogen receptor positive post-menopausal breast cancer cases (NICE, *Early and locally advanced breast cancer: Diagnosis and treatment*, 2009).

Research on AIs, bone loss and osteoporotic fractures

Key UoM researchers:

- **Nigel Bundred** (Senior Lecturer, 1991-1996; Reader, 1996-2001; Professor, 2001-date)
- **Anthony Howell** (Senior Lecturer, 1980-1997; Professor, 1997-date)

Researchers at UoM led three studies (ATAC, ZO-FAST, LIBERATE) that generated important insights around the association between AIs, bone loss and osteoporotic fractures as well as evidence for optimal interventions to prevent bone loss in those treated for breast cancer. Key findings:

1. **Howell** (UK lead, ATAC) and **Bundred** (lead author, chief investigator, ZO-FAST) demonstrated that the complications of using AIs were increased bone loss and subsequent osteoporotic fractures on treatment (1, 2).

2. **Bundred** (lead author, chief investigator) led LIBERATE, the largest international randomised controlled trial of HRT to prevent menopausal symptoms and bone loss in breast cancer patients. Over 3000 women in 31 countries were recruited to LIBERATE. In the bone mineralisation study within LIBERATE, 50% of post-menopausal women with breast cancer were found to be osteopaenic or osteoporotic at diagnosis (3, 4). HRT increased bone mineral density by 3% but also breast cancer recurrence (3), mostly in patients with normal bone mineral density (BMD). There was also a significant increase in breast tumour recurrence in patients randomised to HRT, especially for patients on AIs.

3. Bisphosphonates had been shown to prevent bone loss in osteoporosis. **Bundred** led research to study the effect of bisphosphonates in the setting of hormone receptor positive patients with early breast cancer commencing adjuvant AI therapy with Letrozole. The use of intravenous bisphosphonates prevented bone loss and increased bone density (2). Additionally,

irrespective of BMD, there was a survival advantage for those patients who commenced bisphosphonates from the start of treatment, at analysis 60 months later (5, 6).

3. References to the research

1. **Howell A**, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF, Hoctin-Boes G, Houghton J, Locker GY, Tobias JS. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *The Lancet*. 2005;365(9453):60-2. DOI: 10.1016/S0140-6736(04)17666-6

2. **Bundred NJ**, Campbell ID, Davidson N, DeBoer RH, Eidtmann H, Monnier A, Neven P, von Minckwitz G, Miller JC, Schenk NL, Coleman RE. Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: ZO-FAST study results. *Cancer*. 2008;112(5):1001-10. DOI: 10.1002/cncr.23259

3. Kenemans P, **Bundred NJ**, Foidart J-M, Kubista E, von Schoultz B, Sismondi P, Vassilopoulou-Sellin R, Yip CH, Egberts J, Mol-Arts M, Mulder R, van Os S, Beckmann MW. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. *The Lancet Oncology*. 2009;10(2):135-46. DOI: 10.1016/S1470-2045(08)70341-3

4. **Bundred NJ**, Kenemans P, Yip CH, Beckmann MW, Foidart JM, Sismondi P, Schoultz B, Vassilopoulou-Sellin R, Galta RE, Lieshout EV, Mol-Arts M, Planellas J, Kubista E. Tibolone increases bone mineral density but also relapse in breast cancer survivors: LIBERATE trial bone substudy. *Breast Cancer Research*. 2012;14(1):R13. DOI: 10.1186/bcr3097

5. Eidtmann H, de Boer R, **Bundred N**, Llombart-Cussac A, Davidson N, Neven P, von Minckwitz G, Miller J, Schenk N, Coleman R. Efficacy of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36-month results of the ZO-FAST Study. *Annals of Oncology*. 2010;21(11):2188-94. DOI: 10.1093/annonc/mdq217

6. Eastell R, Adams J, Clack G, **Howell A**, Cuzick J, Mackey J, Beckmann MW, Coleman RE. Long-term effects of anastrozole on bone mineral density: 7-year results from the ATAC trial. *Annals of Oncology*. 2011;22(4):857-62. DOI: 10.1093/annonc/mdq541

4. Details of the impact

See section 5 for corroborating sources S1-S6.

Context

Non-steroidal AIs are now the standard of care for hormone receptor-positive breast cancers in post-menopausal women, nationally and internationally (S1). Our research established that AIs are, however, associated with increases in osteoporotic fractures and increased bone mineral density loss (1, 2). Almost 30,000 post-menopausal women in the UK develop breast cancer annually, 50% of whom already have significant bone mineral density loss before starting treatment. Prior to the research carried out at UoM, 2.3% of those treated with AIs annually developed bone fragility fractures.

Pathways to impact

UoM research has led to the following standards of care now adopted internationally:

1. Routine assessment of BMD using a DEXA scan prior to AI therapy in post-menopausal women with hormone receptor positive breast cancer;
2. Bisphosphonate therapy for all women with a T score < -2;
3. Discontinuation of HRT as a therapeutic intervention after breast cancer diagnosis;
4. Contraindication of HRT in breast cancer patients with menopausal symptoms/bone loss.

Reach and significance of the impact

The research has had a substantial influence on clinical guidelines governing the treatment of breast cancer in the UK and internationally.

Use of DEXA scan and bisphosphonates

As a result of the research, national and international consensus guidelines were issued which indicate the need for pre-adjuvant therapy bone mineral density DEXA scanning to identify patients already osteoporotic or at risk of bone loss (S1-S4). The guidelines ensure commencement of intravenous or oral bisphosphonates where bone loss has been identified or patients have had previous osteoporotic fractures.

The research was cited and adopted in NICE CG80, *Early and locally advanced breast cancer: Diagnosis and treatment* (2009). One of the key priorities identified in these guidelines is that: 'Patients with early invasive breast cancer should have a baseline dual energy X-ray absorptiometry (DEXA) scan to assess bone mineral density if they are starting adjuvant aromatase inhibitor treatment/have treatment-induced menopause/are starting ovarian ablation/suppression therapy' (S1, p. vi). The guidance in the NICE document on treatment with bisphosphonates cites our research, stating: 'Evidence from RCTs (Brufsky, 2006 [S5 below] and **Bundred** et al., 2008 [reference 2 above]) have indicated that in women who were receiving adjuvant letrozole, immediate treatment with zoledronate compared to delayed may prevent loss of BMD at both lumbar spine and total hip. There is evidence that immediate treatment with zoledronic acid maintains the baseline osteopenia status of patients compared with delayed treatment at 12 months [S6 below]. Furthermore, **Bundred** et al. (2008) showed no evidence to suggest a difference in the occurrence of fractures in immediate versus delayed treatment with zoledronate and that there was no difference in breast cancer recurrence when comparing immediate and delayed treatment with zoledronate. There are no significant acute adverse effects with zoledronate.' (S1, p. 68)

The US guidelines (ASCO, S3; NCCN US Task Force Report on Bone Health in Cancer Care, S4) cite our research and advise the use of DEXA scanning and bisphosphonates in patients on aromatase inhibitor therapy after breast cancer treatment.

The guidelines ensure that assessment of BMD using DEXA scan prior to AI therapy is now routine for women with hormone receptor positive breast cancer. Bisphosphonate therapy is now offered to all women with a T score of < -2.

The addition of bisphosphonates has led to a 5-fold reduction in fracture rate to 0.5% annually in patients being treated with AIs. This change in practice, adapted worldwide, has significantly decreased the morbidity and suffering associated with the use of AIs in breast cancer.

HRT use after breast cancer treatment now contraindicated

The NICE guidelines recognise that Tibolone and HRT should not be indicated for the vasomotor symptoms of women with breast cancer and, importantly, that HRT is a less effective treatment than bisphosphonates for women on AIs with breast cancer (S1).

The research has contributed to the discontinuation of HRT as a therapeutic intervention after breast cancer diagnosis. HRT is contraindicated for breast cancer patients with menopausal symptoms or bone loss.

5. Sources to corroborate the impact

S1. NICE/National Collaborating Centre for Cancer. *Early and locally advanced breast cancer: Diagnosis and treatment*. CG80. London: NICE; 2009.

S2. Reid DM, Doughty J, Eastell R, Heys SD, **Howell A**, McCloskey EV, Powles T, Selby P, Coleman RE. Guidance for the management of breast cancer treatment-induced bone loss: A

consensus position statement from a UK Expert Group. *Cancer Treatment Reviews*. 2008;34, Supplement 1(0):S3-S18.

S3. Van Poznak CH, Temin S, Yee GC, Janjan NA, Barlow WE, Biermann JS, Bosserman LD, Geoghegan C, Hillner BE, Theriault RL, Zuckerman DS, Von Roenn JH. American Society of Clinical Oncology Executive Summary of the Clinical Practice Guideline Update on the Role of Bone-Modifying Agents in Metastatic Breast Cancer. *Journal of Clinical Oncology*. 2011;29(9):1221-7.

S4. Gralow JR, Biermann JS, Farooki A, Fornier MN, Gagel RF, Kumar RN, Shapiro CL, Shields A, Smith MR, Srinivas S, Van Poznak CH. NCCN Task Force Report: Bone Health in Cancer Care. *Journal of the National Comprehensive Cancer Network*. 2009;7(Suppl 3):S1-32.

S5. Brufsky A, Harker WG, Beck JT, Carroll R, Tan-Chiu E, Seidler C, et al. Zoledronic Acid Inhibits Adjuvant Letrozole–Induced Bone Loss in Postmenopausal Women With Early Breast Cancer. *Journal of Clinical Oncology*. 2007 March 1, 2007;25(7):829-36.

S6. Gnant M, Mlineritsch B, Luschin-Ebengreuth G, Kainberger F, Kässmann H, Piswanger-Sölkner JC, Seifert M, Ploner F, Menzel C, Dubsky P, Fitzal F, Bjelic-Radisic V, Steger G, Greil R, Marth C, Kubista E, Samonigg H, Wohlmuth P, Mittlböck M, Jakesz R. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy. *The Lancet Oncology*. 2008;9(9):840-9.