Institution: Queen Mary University of London

Unit of Assessment: A1 (Clinical Medicine)

Title of case study: Anastrozole for oestrogen receptor positive breast cancer

1. Summary of the impact

Approximately 80% of all breast cancer is hormone receptor positive localised cancer in postmenopausal women. For 30 years the universal standard adjuvant endocrine treatment for these women was five years of tamoxifen, but side effects and recurrences limited its usefulness. Results from the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial led to a major worldwide change in the standard recommended treatment, from tamoxifen to anastrozole (an aromatase inhibitor). From 2009 this treatment became UK national policy (recommended by NICE), and guidance in other countries (eg Australia, USA) has also been revised. Anastrozole is now routinely offered to women with hormone receptor positive breast cancer in UK and (extrapolating from trial data) we estimate over a thousand are spared a recurrence in UK annually.

2. Underpinning research

Breast cancer is the commonest cancer in the UK, with a substantial burden of morbidity and mortality. The ATAC study, the first and largest double-blind randomised trial to compare the efficacy and safety of anastrozole, tamoxifen or both as treatment for oestrogen receptor positive breast cancer in postmenopausal women, was conducted in 381 centres in 21 countries, and studied 9,366 women over five years. Recruitment began in 1996 and closed in 2000. Participants were postmenopausal women over 45 who had completed primary surgery and chemotherapy for invasive breast cancer and who were candidates for hormone therapy. Long-term follow-up showed a 24% reduction in 10-year recurrence rates with anastrozole beyond that achieved with tamoxifen. The paper presenting the main results, published in the Lancet in 2005, has been cited over 1,600 times [1].

Professor Jack Cuzick (Head of Centre 1998 - present) was the trial statistician from the outset, and as a founding member of the Trial Steering Committee helped to design the trial. He conducted all analyses of the trial data in conjunction with other QMUL staff including Christopher Wale (Research Fellow 1998-2010), and Ivana Sestak (Research Fellow 2003-present). Professor Cuzick is the Principal Investigator for the continued long-term follow-up of this trial. All analyses were conducted by Prof Cuzick's group, which was the only group with access to treatment codes.

A significant component of the analytic work for the trial was statistical analysis, including major retrospective studies of treatment effects. In addition to studies of the primary efficacy end-point (disease free survival) [1,2], side effect profile [3,4] and long-term follow-up [5], two major sub-studies were conducted within the trial: on bone changes [6] and quality of life [7]. In addition, a new prognostic model for recurrence has been developed [8].

The main findings to date can be summarised as follows:

1. Anastrozole is more effective and better tolerated than tamoxifen in preventing recurrence and distant recurrence of breast cancer. ATAC was the first study to report this finding in the adjuvant setting [1]. The most recent 10-year analysis confirms continued superiority of anastrozole over a sustained time interval [5].
2. Anastrozole over a 10-year period is substantially more effective than tamoxifen in preventing new tumours in the opposite breast (hazard ratio 0.68 overall, 0.62 for hormone receptor-positive tumours), suggesting it could prevent 75% of oestrogen receptor positive cancers in high-risk women who do not have cancer [5].
3. The combination of anastrozole and tamoxifen is no more effective than tamoxifen alone, and significantly less effective than anastrozole alone [1,6]. This is due to the agonist properties of tamoxifen (reduces oestrogen suppression).
4. Bone loss occurs during treatment but recovers soon after stopping, so that only women who start with a low bone density need to be given bisphosphonate treatment. With this protocol,

the risk of increased fracture rates in women taking aromatase inhibitors is minimal [6].

5. By contrast with tamoxifen, anastrozole is not associated with any increase in endometrial cancer, other gynaecologic symptoms, or thromboembolic events [3].
6. Carpal tunnel syndrome is a rare but real side effect of aromatase inhibitor treatment, but most cases are mild, do not need surgery and resolve spontaneously after treatment cessation [9].
7. Quality of life is similar in patients treated with tamoxifen or anastrozole [7].

3. References to the research

Nine publications are shown of more than 30 total. QMUL staff in **bold.**

1. Howell A, **Cuzick J**, Baum M, Buzdar A, Dowsett M, Forbes JF, Hoctin-Boes G, Houghton J, Locker GY, Tobias JS. ATAC Trialists' Group. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005; 365: 60-62. (Correspondence: Lancet 2005; 365: 1225-1226).
2. Dowsett M, **Cuzick J, Wale C**, Forbes J, Mallon EA, Salter J, Quinn E, Dunbier A, Baum M, Buzdar A, Howell A, Bugarini R, Baehner FL, Shak S. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. *J Clin Oncol* 2010; 28:1829-34
3. The ATAC Trialists' Group: Buzdar A, Howell A, **Cuzick J, Wale C,** Distler W, Hoctin-Boes G, Houghton J, Locker GY, Nabholtz JM. Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial. *Lancet Oncology* 2006; 7: 633-4
4. **Cuzick J, Sestak I**, Cella D, Fallowfield L; on behalf of the ATAC Trialists' Group. Treatment-emergent endocrine symptoms and the risk of breast cancer recurrence: a retrospective analysis of the ATAC trial. *Lancet Oncology* 2008; 9:1143-48.
5. **Cuzick J, Sestak I**, Baum M, Buzdar A, Howell A, Dowsett M, Forbes JF, on behalf of the ATAC/LATTE investigators. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. *Lancet Oncology* 2010; 11: 1109-10.
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: 857-62*.*
7. Fallowfield L, Cella D, **Cuzick J**, Francis S, Locker G, Howell A. Quality of life of postmenopausal women in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Adjuvant Breast Cancer Trial. *Journal of Clinical Oncology* 2004; 22: 4261-71.
8. **Cuzick J**, Dowsett M, Pineda S, Wale C, Salter J, Quinn E, Zabaglo L, Mallon E, Green AR, Ellis IO, Howell A, Buzdar AU, Forbes JF. Prognostic value of a combined estrogen receptor, progesterone receptor, Ki-67, and human epidermal growth factor receptor 2 immunohistochemical score and comparison with the Genomic Health recurrence score in early breast cancer. *Journal of Clinical Oncology* 2011; 29: 4273-78.
9. Sestak I, Sapunar F, **Cuzick J**. Aromatase inhibitor-induced carpal tunnel syndrome: results from the ATAC trial. *Journal of Clinical Oncology* 2009; 27: 4961-5.

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4. Details of the impact

Publication of the results of the ATAC trial, (five-year follow up in 2005, 10-year follow up in 2010), supported by results from other international trials that confirmed our findings, led to a major change worldwide in the treatment of women with postmenopausal oestrogen receptor positive breast cancer. This research [a] established beyond doubt the most efficacious treatment for preventing recurrence; [b] quantified the benefits; [c] documented and quantified the side effects; and [d] showed how the major side effects can be most effectively managed in different sub-groups of women. The impact of these results can be observed in policy/guidelines; clinical practice; and changes in morbidity and mortality.

4a: Change in policy / guidelines

Three examples are given from numerous policies and guidelines around the world:

- **UK:** In 2009 the NICE guidance for treatment of women with hormone receptor-positive breast cancer was changed to five years of an aromatase inhibitor as the treatment of choice. See [10,11] and BMJ summary reference [12] below.
- **USA:** By 2006, three leading professional organisations (the National Comprehensive Cancer Network Breast Cancer Clinical Practice Guidelines in Oncology, the American Society of Clinical Oncology Technology Assessment on the Use of Aromatase Inhibitors, and the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer) had all changed their guidance to incorporate the results of the ATAC trial. However, at that stage the recommendation reflected that no overall increase in survival had yet been shown, and anastrozole was considered to be 'equivalent' to tamoxifen [13]. In 2010, on publication of the 10-year follow-up of ATAC (which did show a statistically significant benefit on mortality), the ASCO task force updated its guidelines [14], recommending that most postmenopausal women with hormone receptor-positive breast cancer consider incorporating aromatase inhibitor therapy in adjuvant treatment.
- **Australia:** Government-issued guidance for treatment for post-menopausal women with hormone receptor positive early breast cancer favours anastrozole over tamoxifen [15].

4b: Change in clinical practice

Anastrozole is widely used throughout the world, with over 5.9 million patient years of medication recorded [16]. For example:

- **UK:** Standard clinical practice in every oncology unit in the UK reflects NICE guidance, which incorporates the ATAC findings. Depending on clinical circumstances – eg the individual balance between risk of endocrine side effects (commoner with tamoxifen) and bone side effects (commoner with anastrozole) – anastrozole is now routinely offered to post-menopausal women with hormone receptor-positive breast cancer [17].
- **USA:** Health Maintenance Organisations in USA fund anastrozole in suitable patients. See for example [18].
- **Australia:** Anastrozole is now approved (registered and subsidised by the Pharmaceutical Benefits Scheme) for use in women with hormone receptor-positive breast cancer. More than a million Australian women have received this treatment regimen.
- **Germany:** A study of prescribing patterns among oncologists and gynaecologists in Germany [19] concluded in 2008 that treatment with aromatase inhibitors had increased dramatically and had effectively replaced the previous gold standard treatment, tamoxifen.

4c: Change in morbidity and mortality (time to recurrence and side effects)

Sine the 10-year follow-up of the ATAC trial was only published in 2010, insufficient time has passed to follow up non-trial subjects long-term. Over 10 years, around 80% of ATAC participants taking anastrozole were still cancer free, compared with 76% of those on the previous gold standard treatment of tamoxifen. Anastrozole causes significantly fewer side effects than

tamoxifen, and is not associated with any increase in endometrial cancer, other gynaecologic symptoms or thromboembolic events. Extrapolating from the trial data, we anticipate that since around 32,000 postmenopausal women are diagnosed annually with breast cancer in the UK, this is likely to translate to over a thousand fewer women developing a recurrence of their breast cancer or experiencing unnecessary side effects from their medication each year.

5. Sources to corroborate the impact

10. NICE Guideline 2009. 'Breast cancer (early and locally advanced): diagnosis and treatment' www.nice.org.uk/CG80 (reviewed 2012 and confirmed still current).
11. NICE Guideline 2009 'Advanced breast cancer: diagnosis and treatment' www.nice.org.uk/CG81 (reviewed 2012 and confirmed still current).
12. Harnett *et al*. Diagnosis and treatment of early breast cancer, including locally advanced disease—summary of NICE guidance. *BMJ* 2009; 338: b438. doi: 10.1136/bmj.b438 www.ncbi.nlm.nih.gov/pmc/articles/PMC3266859/
13. St Gallen Consensus Statement on Breast Cancer Treatment. *Journal of National Comprehensive Cancer Network* 2006; 4: 971-9. www.ncbi.nlm.nih.gov/pubmed/17112447
14. Burstein HJ, Prestrud AA, Seidenfeld J. American Society of Clinical Oncology Clinical Practice Guideline Update on Adjuvant Endocrine Therapy for Women With Hormone Receptor-Positive Breast Cancer. *Journal of Clinical Oncology* 2010; 28: 3784-3796. PMID: 20625130.
15. Australian government recommendations for aromatase inhibitors as adjuvant endocrine therapy in oestrogen receptor-positive breast cancer: http://guidelines.nbocc.org.au/guidelines/adjuvant_endocrine_therapy/
16. Manufacturer's audit of sales (Astra Zeneca file ADX2810102): www.arimdex.net/arimidex-prescribing-information/
17. Example of UK-based clinical protocol: Royal Marsden Hospital protocol for adjuvant treatment in oestrogen receptor-positive breast cancer recommends aromatase inhibitor: www.royalmarsden.nhs.uk/SiteCollectionDocuments/gp-education/20110722/mark-allen.pdf
18. Example of US Health Maintenance Organization policy on this topic (Kaiser Permanente): www.permanente.net/homepage/kaiser/pdf/66383.pdf
19. Luftner D, Scheller J, Kolm P, Possinger K. Prescription pattern of aromatase inhibitors for the adjuvant therapy of breast cancer in Germany – Results of the second survey among gynaecologists and medical oncologists. *Onkologie* 2008; 31: 19-25.