Institution: University College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Introduction of aromatase inhibitors for the treatment of breast cancer

1. Summary of the impact

The ATAC trial was conceived, designed and implemented by UCL investigators, and has resulted in a dramatic, global change in the management of breast cancer. It directly compared tamoxifen, the standard treatment for breast cancer for 25 years, with anastrozole, a novel aromatase inhibitor. It convincingly demonstrated superiority for the new agent, in terms of both progression-free survival and adverse effect profile. Tamoxifen had been the world's most widely prescribed anti-cancer drug but was supplanted by anastrozole as a consequence of this trial.

2. Underpinning research

Breast cancer is the most common form of cancer in the UK, with around 50,000 new diagnoses annually, and the second most common cause of cancer death in women (approximately 12,000 deaths per year). Almost all newly diagnosed women will undergo hormone manipulation therapy to block the effects of endogenous oestrogen. Until the introduction of the aromatase inhibitors, the principal oestrogen antagonist was tamoxifen.

The ATAC trial was based on the recognition that aromatase inhibitors, a novel class of breast cancer agents, had theoretical advantages over tamoxifen **[1]**. Tamoxifen was used after surgery for breast cancer, and known to reduce the risk of recurrent disease; it works via blockade of oestrogen receptors in breast tissue. The essential benefit of aromatase inhibitors is that they block all extra-ovarian post-menopausal production of oestrogens, the synthesis of which depends on metabolism of testosterone and androstenedione by the aromatase enzyme. This represented a fundamental approach to oestrogen deprivation, in contrast to tamoxifen which only blocked oestrogen *uptake* at the cellular level while leaving its *production* unchanged.

At the time the ATAC trial was designed, there was considerable resistance to the concept of novel therapy using anastrozole alone, since tamoxifen was already so well established and indeed was the world's most widely prescribed anti-cancer drug. UCL investigators took the view that, although tamoxifen was an effective and relatively safe drug, it was not without hazards, some of which could be life-threatening. The ATAC trial was the first to offer a 'head to head' comparison with tamoxifen, both alone (single agent) and in combination, and demonstrated that the newer agent was both more effective and less toxic **[1-5]**.

The ATAC trial recruited 6,241 patients, with long-term follow-up of approximately 24,000 woman-years **[3, 4]**. Anastrozole reduced the absolute risk of recurrence of breast cancer by 3% compared to tamoxifen, and treatment-related serious adverse events by 5%.

3. References to the research

[1] Baum M, Budzar AU, Cuzick J, Forbes J, Houghton JH, Klijn JG, Sahmoud T; ATAC Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet. 2002 Jun 22;359(9324):2131-9. http://dx.doi.org/10.1016/S0140-6736(02)09088-8

[2] 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 Jan 1-7;365(9453):60-2. http://dx.doi.org/10.1016/S0140-6736(04)17666-6

[3] Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group, Forbes JF, Cuzick J, Buzdar A, Howell A, Tobias JS, Baum M. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. Lancet Oncol. 2008 Jan;9(1):45-53. http://dx.doi.org/10.1016/S1470-2045(07)70385-6

[4] Cuzick J, Sestak I, Baum M, Buzdar A, Howell A, Dowsett M, Forbes J; ATAC/LATTE investigators. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. Lancet. 2010 Dec;11(12):1135-41. http://dx.doi.org/10.1016/S1470-2045(10)70257-6

[5] Ring A, Sestak I, Baum M, Howell A, Buzdar A, Dowsett M, Forbes JF, Cuzick J. Influence of comorbidities and age on risk of death without recurrence: a retrospective analysis of the Arimidex, Tamoxifen Alone or in Combination trial. J Clin Oncol. 2011 Nov 10;29(32):4266-72. http://dx.doi.org/10.1200/JCO.2011.35.5545

Funder: Cancer Research UK

Sponsor: University College London

4. Details of the impact

ATAC was the first trial to show that an aromatase inhibitor alone is more effective than tamoxifen for adjuvant treatment of early breast cancer, with fewer adverse effects. This has now been confirmed by subsequent studies **[a, b, c]**. ATAC has been the only trial to perform a direct head-to-head comparison of anastrozole against tamoxifen alone. The trial has the longest duration of follow-up, with benefits of anastrozole maintained out to at least 10 years. Anastrozole is now the most widely prescribed aromatase inhibitor worldwide, with more than twice as many prescriptions annually as the next most widely prescribed aromatase inhibitor. Over 5.5 million patient years of experience with anastrozole has now accrued, and global sales totalled $2.8bn for the period 2010-12, with the manufacturers citing the ATAC trial as the basis of this success **[d]**.

National and international guidelines now advocate use of an aromatase inhibitor as first-line adjuvant therapy instead of tamoxifen, based principally on the results of the ATAC trial. In 2005, a technology assessment from the American Society of Clinical Oncology on the use of aromatase inhibitors as adjuvant therapy for post-menopausal women with hormone receptor-positive early-stage breast cancer recommended that: "*Based on results from multiple large randomized trials, adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer should include an aromatase inhibitor in order to lower the risk of tumor recurrence*" **[e]**. The document refers to the ATAC trial throughout. The following year, a NICE technology assessment recommended that "*The aromatase inhibitors anastrozole, exemestane and letrozole, within their licensed indications, are recommended as options for the adjuvant treatment of early oestrogen-receptor-positive invasive breast cancer in postmenopausal women*" **[f]**. In March 2009, NICE Clinical Guideline 80 on 'Early and locally advanced breast cancer' recommended that "*Postmenopausal women with ER-positive early invasive breast cancer who are not considered to be low risk should be offered an aromatase inhibitor, either anastrozole or letrozole, as their initial adjuvant therapy*" **[g]**. This was listed as a key priority.

Anastrozole is now become standard treatment. A commentary on our 10-year analysis (ref [4] above) in the Lancet Oncology in 2010 stated that "*Mainly on basis of the initial results of ATAC, aromatase inhibitor treatment has now been declared the standard adjuvant treatment of endocrine-responsive breast cancer by the St Gallen International Expert Consensus*" **[h]**.

Anastrozole offers significant benefits to patients. While anastrozole and tamoxifen demonstrate similar outcomes in terms of overall survival, anastrozole increased absolute progression-free survival by 3%. Patients were also less likely to stop treatment because of treatment-related adverse effects. The following adverse effects were less common with anastrozole than with tamoxifen: hot flushes (5% absolute risk reduction), vaginal bleeding (5%) or discharge (9%),

venous thrombosis (2%), stroke (1%) and endometrial cancer (0.4%) **[i]**.

Anastrozole has been estimated to lead to 0.26 QALYs gained per patient, with an incremental cost-effectiveness ratio of approximately £12,600 per QALY gained and £14,700 per life-year gained **[j]**.

5. Sources to corroborate the impact

[a] Aydiner A, Tas F. Meta-analysis of trials comparing anastrozole and tamoxifen for adjuvant treatment of postmenopausal women with early breast cancer. Trials 2008;9:47. http://dx.doi.org/10.1186/1745-6215-9-47

[b] Eisen A, Trudeau M, Shelley W, Messersmith H, Pritchard KI. Aromatase inhibitors in adjuvant therapy for hormone receptor positive breast cancer: a systematic review. Cancer Treatment Rev 2008;34:157-74. http://dx.doi.org/10.1016/j.ctrv.2007.11.001

[c] Gibson L, Lawrence D, Dawson C, Bliss J. Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women (Review). Cochrane Database Syst Rev 2009;(4). http://dx.doi.org/10.1002/14651858.CD003370.pub3.

[d] http://www.astrazeneca-annualreports.com/2012/documents/eng_download_centre/annual_report.pdf. Sales figures p.65. ATAC trial mentioned p.66 as follows: "*Arimidex, first launched in 1995, remains a leading global hormonal therapy for patients with early breast cancer. This success is largely based on the extensive long-term efficacy and safety results of the ATAC study, which showed Arimidex to be significantly superior to tamoxifen at preventing breast cancer recurrence during and beyond the five year treatment course*."

[e] Winer EP, Hudis C, Burstein HJ, Wolff AC, Pritchard KI, Ingle JN, Chlebowski RT, Gelber R, Edge SB, Gralow J, Cobleigh MA, Mamounas EP, Goldstein LJ, Whelan TJ, Powles TJ, Bryant J, Perkins C, Perotti J, Braun S, Langer AS, Browman GP, Somerfield MR. American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for post-menopausal women with hormone receptor-positive early-stage breast cancer: status report 2004. J Clin Oncol 2005; 23:9-29. http://dx.doi.org/10.1200/JCO.2005.09.121

[f] http://guidance.nice.org.uk/TA112/Guidance/pdf/English

[g] http://www.nice.org.uk/nicemedia/live/12132/43413/43413.pdf See p. 6 for key priority recommendation. Three of our papers are referenced extensively, along with another two papers from the ATAC group of investigators.

[h] Gnant M. 10 years of ATAC: one question answered, many others unresolved. Lancet Oncol. 2010 Dec;11(12):1109-10. http://dx.doi.org/10.1016/S1470-2045(10)70270-9.

[i] http://www.macmillan.org.uk/Cancerinformation/Cancertreatment/Treatmenttypes/Hormonaltherapies/Individualhormonaltherapies/Anastrozole.aspx

[j] Locker GY, Mansel R, Cella D, Dobrez D, Sorensen S, Gandhi SK, on behalf of the ATAC Trialists' Group. Cost-effectiveness analysis of anastrozole versus tamoxifen as primary adjuvant therapy for postmenopausal women with early breast cancer: a US healthcare system perspective. The 5-year completed treatment analysis of the ATAC ('Arimidex', Tamoxifen Alone or in Combination) trial. Breast Cancer Res Treat 2007;106:229-238. http://dx.doi.org/10.1007/s10549-006-9483-6