Aromatase Inhibitors in Metastatic Breast Cancer

a report by
J Michael Dixon

Consultant Surgeon and Senior Lecturer in Surgery, Edinburgh Breast Unit, Western General Hospital, UK

DOI: 10.17925/EOH.2006.0.2.16

J Michael Dixon is a consultant surgeon and senior lecturer at the Edinburgh Breast Unit, Western General Hospital, which treats almost 750 newly diagnosed breast cancers every year. He trained in Edinburgh and Oxford. Mr Dixon is a fellow of The Royal College of Surgeons of both Edinburgh and England and an honorary fellow of The Royal College of Physicians of Edinburgh. His research focuses on surgical perspectives in neoadjuvant endocrine therapy of large operable and locally advanced breast cancer, particularly aromatase inhibitor treatment. Mr Dixon received his MBChB and MD degrees from Edinburgh University, and also has a first class BSc in Pathology. Dr Dixon has published over 200 papers, contributed to 68 book chapters, and written or edited 16 books. He was the inaugural managing editor of *The Breast* and a former member of the editorial board of *British Medical Journal*. Dr Dixon has also given over 150 invited lectures all around the world.

Until recently, the aim of treatment for advanced or metastatic breast care (ABC) was to produce effective control of symptoms with minimum side effects.[1] The aim has changed with the introduction of newer, more effective systemic treatments, and now optimal therapy prolongs survival and maintains quality of life. Options for systemic therapy include: chemotherapy, hormonal therapy and trastuzumab in patients with human epidermal growth factor receptor 2 (HER2) positive cancers.[2]

Anti-oestrogen therapy with tamoxifen has been the standard first-line treatment for postmenopausal women with hormone receptor-positive (HR+) ABC for over two decades, offering efficacy with minimal acute toxicity compared with chemotherapy.[3] Unfortunately, disease progression and resistance to tamoxifen develops in one half of those who respond by 18 months.[4] The search for superior therapeutic alternatives to tamoxifen led to development of three generations of aromatase inhibitors (AIs), agents that prevent the synthesis of oestrogen. Third-generation AIs have now been shown to be superior to tamoxifen in the first-line metastatic setting or better than alternative agents following tamoxifen failure and are now the preferred choice for postmenopausal patients with HR+ ABC.[5-9] This editorial reviews findings from studies with the third-generation AIs and discusses the developing option of sequential use of hormonal agents in the treatment of HR+ ABC patients.

AI Studies in the First-line Setting

Anastrozole

The two trials that compared anastrozole with tamoxifen were prospectively designed to demonstrate equivalence between the two agents (European trial [N=668][10] and North American trial [N=353].[11]) The European study found no difference between anastrozole and tamoxifen in the primary end-point of median time to progression (TTP), (8.2 months vs 8.3 months; p=0.941), or in overall response rate (ORR) (32.9% vs 32.6%).[10] The smaller North American study also demonstrated a similar ORR between the treatment arms (21% anastrozole vs 17% tamoxifen) but an improved TTP for anastrozole (11.1 months vs 5.6 months; p=0.005).[11] A combined analysis of both studies was performed despite differences in demographics and baseline characteristics and failed to show any significant benefit for anastrozole in TTP in the overall population, but did show a benefit in TTP for the subset of HR+ patients.[7] At 44 months of follow-up, there was no difference in survival between anastrozole and tamoxifen from the combined analsysis.[12]

Letrozole

One large trial (PO25) compared letrozole with tamoxifen (N = 907) until appearance of progressive disease.[8,13] Crossover treatment was allowed after progression in a double-blind fashion. Patients receiving letrozole (n = 458) had a significantly longer median TTP (9.4 months vs 6.0 months; p<0.0001) compared with tamoxifen (n = 458). Letrozole prolonged TTP by 57% and significantly reduced the risk of progression by 30% (p=0.0001).[8,13] A multivariate analysis of TTP, adjusted for key baseline covariates of receptor status, prior adjuvant therapy and dominant site of disease, confirmed the superiority of letrozole over tamoxifen in reducing the risk of progression in all groups (all p=0.0001).[13]

ORR was significantly higher for letrozole vs tamoxifen (32% vs 21%, p=0.0002) as was the rate of complete response (9% vs 3%, p=0.0004). A stratified analysis of ORR, adjusted for the same covariates used in the analysis of TTP, confirmed that letrozole significantly increased the odds of achieving a complete response or partial response when compared with tamoxifen (p=0.0002).[13] Time to chemotherapy was significantly longer (p=0.005) in patients whose initial treatment was letrozole (16.3 months vs 9.3 months). Although median overall survival (OS) was prolonged for patients in the letrozole arm (34 months vs 30 months), this difference was not significant. A prospectively planned analysis of survival at six-month intervals showed that letrozole was significantly superior to tamoxifen over the first

24 months.[8] In an exploratory analysis of OS in the 448 patients who did not cross over to the alternate drug at progression, there was a median survival benefit of 15 months in patients receiving letrozole as their first treatment (median survival was 35 months in the letrozole group and 20 months in the tamoxifen group).[8,14]

Exemestane

The European Organisation for Research and Treatment of Cancer (EORTC) evaluated exemestane in patients with ABC (N = 382) in a randomized phase III trial. Treatment with exemestane prolonged progression-free survival compared with tamoxifen (9.9 months, 95% confidence interval [CI] = 8.7–11.8 months vs 5.8 months, 95% CI = 5.3–8.1 months, respectively) and had significantly higher objective response rates (46% vs 31%, p=0.005);[9] further details await full publication of the results.

Third-generation AIs have now been shown to be superior to tamoxifen in the first-line metastatic setting or better than alternative agents following tamoxifen failure.

Summary

In summary, exemestane and letrozole have a superior ORR when compared with tamoxifen.[8,9] Letrozole is superior to tamoxifen for all end-points, and there is an early survival benefit for letrozole.[8,13] With anastrozole the North American trial (N = 353) showed a significantly prolonged time to recurrence when compared with tamoxifen, but the European study (N = 668 patients), which enrolled nearly twice as many patients, did not.[10,11] The combined analysis of these two studies (N = 1,021) showed no significant benefit in TTP for anastrozole in the whole population, although there was a small but significant benefit in HR+ patients.[7]

AI Studies in the Second-line Setting

All three AIs have been compared with the known standard second-line therapies. Two trials, both powered to show equivalence, compared anastrozole to megestrol acetate (MA).[15,16] Similar to findings of the first-line studies, significant results were only apparent in one of the two trials with a combined retrospective analysis of both trials showing a significant survival advantage for anastrozole (p=0.0248).[15-17] A trial of exemestane and MA also powered to show equivalence found exemestane to be superior to MA with median TTP (4.7 vs 3.9 months, p=0.037) and time to treatment failure (TTF) (3.8 months vs 3.7 months, p=0.042).[18] Letrozole demonstrated better efficacy and longer disease control and improved safety over both aminoglutethimide (AG) and MA in several multicenter comparisons.[5,6,19] In the only head-to-head comparison of anastrozole and letrozole in the second-line setting, TTP, the primary end-point was similar between the two groups. Although letrozole demonstrated a significantly higher ORR than anastrozole (p=0.012), a significant clinical benefit over anastrozole was seen only in the large oestrogen receptor (ER)-unknown subgroup (n = 340) with no significant difference in the ER-positive population.[20] Although letrozole is a more effective aromatase inhibitor than anastrozole[21], this direct head-to-head comparison did not demonstrate consistent superiority of letrozole over anastrozole in clinical efficacy.

Safety and Quality of Life

AIs have superior safety and tolerability profiles when compared with alternative agents. All phase III trials of postmenopausal women with ABC resistant to tamoxifen have reported fewer adverse events with AIs. MA results in more weight gain, sweating, dyspnoea, vaginal haemorrhage and hypertension; the most common serious adverse events attributable to MA include cardiovascular events, stroke and pulmonary embolism.[6,16,18,19,22] In contrast, hot flushes are experienced more often with AIs than with MA.[6,16,18,19,22]

To directly compare the two non steroidal AIs, a small crossover-design preference study comparing preferences and quality of life (QoL) ratings after four weeks of anastrozole and four weeks of letrozole treatment in patients who had prior tamoxifen reported fewer reports of adverse events in patients taking letrozole compared to those taking anastrozole (43% vs 65%; p=0.0028).[23] Patients taking letrozole had the highest QoL ratings (p=0.02), and twice as

many patients preferred to continue with letrozole when given a choice (68% vs 32%, P<0.01).[23] This small study needs validation with more patients and treatment durations of at least three months because it is clear that one month is insufficient to compare QoL changes accurately.

In the first-line setting, AIs have demonstrated better tolerability than tamoxifen. In the combined analysis of two first-line anastrozole vs tamoxifen studies, the frequency of adverse events was comparable in both groups, demonstrating that anastrozole is at least as safe as tamoxifen.[19] Anastrozole was associated with significantly fewer thromboembolic events (4% vs 7%; p=0.043) and a trend towards less lethargy (1% vs 3%, p=0.075) and vaginal bleeding (1% vs 2%, p=0.207), but more vaginal dryness (2% vs 1%, p=0.089). Hot flushes were marginally fewer in the tamoxifen group than in the anastrozole group (27% vs 23%, p=0.218).[19] In contrast, first-line exemestane was associated with lower incidences of bone pain (12% vs 18%) and hot flushes (5% vs 12%) when compared with tamoxifen.[9]

AIs have superior safety and tolerability profiles when compared with alternative agents.

Letrozole increased quality time without symptoms or toxicity in patients with ABC, and patients experienced fewer serious adverse events such as thromboembolic events (1% vs 2%) and anorexia (4% vs 6%) and provided a longer chemotherapy-free interval.[13,14] Another more recent study confirmed that letrozole increased time to disease progression without extending time with adverse events and even offered prolonged quality-adjusted survival for patients when compared with tamoxifen.[24]

Sequential Use of Hormonal Agents

The anti-oestrogens and AIs have different mechanisms of action, so previous resistance to tamoxifen does not preclude a response to AI therapy. All three AIs are approved for therapy in the second-line setting following tamoxifen failure because they are effective in patients with visceral disease, show little or no cross-reactivity with tamoxifen, and are more active and safer than AG or MA. However, as anastrozole and letrozole are approved in the first-line setting and are clearly the first-line treatments of choice, the present issue is what to use as a second-line agent following disease progression with an AI. Although the efficacy of AIs has been demonstrated after tamoxifen failure, the question of whether additional responses can be achieved after a first failure with tamoxifen and a second failure with a non-steroidal AI remains.

Fulvestrant is a serum oestrogen receptor (ER) downregulator, a new type of ER antagonist with no agonist effects.[25] In preclinical studies, fulvestrant has been shown to be active and potent against tamoxifen-resistant cells.[26] The efficacy of fulvestrant was evaluated in two head-to-head trials against anastrozole in postmenopausal women with tamoxifen-resistant metastatic breast cancer.[27,28] No statistically significant differences could be demonstrated in any of the outcome measures in either trial, although there was a numerically superior TTP (5.4 months vs 3.4 months) and median duration of response (19 months vs 10.8 months) for fulvestrant in one trial.[28] A prospectively planned, combined analysis showed that fulvestrant was similar to anastrozole with respect to OS in the second-line setting.[29] This steroidal, pure anti-oestrogen is approved as endocrine therapy for patients with HR+ metastatic breast cancer with disease progression following tamoxifen therapy.

Evaluations of sequential hormone therapy have found small but consistent responses regardless of the order in which therapy was administered,[30-33] indicating that patients with hormone-sensitive breast cancer benefit from sequential administration of available hormone agents. Sequential administration of first-line anastrozole followed by tamoxifen and vice versa has been shown to be similarly effective.[30] There is also some suggestion that the partial non-cross-resistance between steroidal and nonsteroidal antiaromatase agents is independent of the sequence employed.[32] Exemestane has demonstrated efficacy in some patients after first-line tamoxifen failure or following second-line therapy failure with a nonsteroidal AI.[31] Patients who receive exemestane as their first anti-aromatase agent can still benefit from letrozole or anastrozole after disease progression.[32] Similarly, patients who progress on treatment with

fulvestrant may retain sensitivity to other endocrine agents.[33] There are on-going studies investigating whether after non-steroidal AI failure exemestane or fulvestrant should be used.

Recent interest in giving oestrogen after AI and fulvestrant failure has been aroused by laboratory data showing that after oestrogen withdrawal, resistant cancer cells are killed by treatment with oestrogen.[34] There is now the theoretical option of resensitising cells with oestrogen in such patients and re-administering an AI in combination with fulvestrant.[34]

Conclusion

All three third-generation AIs have shown superior efficacy and tolerability when compared with tamoxifen, MA, or AG, but it is not clear whether efficacy differences exist among these three.[14,35,36] The results from the trial comparing letrozole and tamoxifen in the first-line setting are more impressive than the results in the studies comparing anastrozole or exemestane with tamoxifen. Sequential use of hormonal agents is being investigated and may prolong the usage of endocrine therapies and avoid the introduction of cytotoxic chemotherapy and its associated acute toxicities into the treatment regimen. The treatment of ABC has clearly improved with the development of AIs. The AIs offer safer, more efficacious treatment and are rapidly becoming the preferred therapy for postmenopausal patients with HR+ ABC. ■

References

1. *Leonard RCF, Rodger A, Dixon JM, "Metastatic Breast Cancer" Dixon JM (ed),* ABC of Breast Diseases, *(1995), London: BMJ Books Publishing Group, pp. 65–71.*
2. *Solomayer EF, Diel IJ, Meyberg GC, et al.,* Breast Cancer Res Treat *(2000);59: pp. 271–278.*
3. *Hamilton A, Piccart M,* Ann Oncol *(1999);10: pp. 377–384.*
4. *Dorssers LC, Van der Flier S, Brinkman A, et al.,* Drugs *(2001);61: pp. 1721–1733. Review.*
5. *Gershanovich M, Chaudri HA, Campos D, et al.,* Ann Oncol *(1998);9: pp. 639–645.*
6. *Dombernowsky P, Smith I, Falkson G, et al.,* J Clin Oncol *(1998);16: pp. 453–461.*
7. *Bonneterre J, Buzdar A, Nabholtz JM, et al.,* Cancer *(2001);92: 2247–2258.*
8. *Mouridsen H, Gershanovich M, Sun Y, et al.,* J Clin Oncol *(2003);21: pp. 2101–2109.*
9. *Paridaens R, Therasse P, Dirix L, et al.,* Proc Am Soc Clin Oncol *(2004);22(Suppl 14): Abstract 515.*
10. *Bonneterre J, Thurlimann B, Robertson JF, et al.,* J Clin Oncol *(2000);18: 3748–3757.*
11. *Nabholtz JM, Buzdar A, Pollak M, et al.,* J Clin Oncol *(2000);18: pp. 3758–3767.*
12. *Nabholtz JM, Bonneterre J, Buzdar A, et al.,* Eur J Cancer *(2003);39: pp. 1684–1689.*
13. *Mouridsen H, Gershanovich M, Sun Y, et al.,* J Clin Oncol *(2001);19: pp. 2596–2606.* Erratum in: J Clin Oncol *(2001);19: p. 3302.*
14. *Femara prescribing information, Novartis Pharmaceuticals Corp, East Hanover, New Jersey, December 2005.*
15. *Buzdar AU, Jones SE, Vogel CL, et al.,* Cancer *(1997);79: pp. 730–739.*
16. *Jonat W, Howell A, Blomqvist C, et al.,* Eur J Cancer *(1996);32A: pp. 404–412.*
17. *Buzdar AU, Jonat W, Howell A, et al.,* Cancer *(1998);83: pp. 1142–1152.* Erratum in: Cancer *(1999);85: p, 1010.*
18. *Kaufmann M, Bajetta E, Dirix LY, et al.,* J Clin Oncol *(2000);18: pp. 1399–1411.*
19. *Buzdar A, Douma J, Davidson N, et al.,* J Clin Oncol *(2001);19: pp. 3357–3366.*
20. *Rose C, Vtoraya O, Pluzanska A, et al.,* Eur J Cancer *(2003);39: pp. 2318–2327.*
21. *Bhatnagar AS,* Br J Cancer *(2005);92: 1173–1174.*
22. *Buzdar A, Jonat W, Howell A, et al.,* J Clin Oncol *(1996);14: pp. 2000–2011.*
23. *Thomas R, Godward S, Makris A, et al.,* Clin Oncol *(R Coll Radiol) (2004);16: pp. 485–491.*
24. *Irish W, Sherrill B, Cole B, et al.,* Ann Oncol *(2005);16: pp. 1458–1462.*
25. *Wakeling AE, Dukes M, Bowler J,* Cancer Res *(1991);51: pp. 3867–3873.*
26. *Osborne CK, Coronado-Heinsohn EB, Hilsenbeck SG, et al.,* J Natl Cancer Inst *(1995);87: pp. 746–750.*
27. *Howell A, Robertson JF, Quaresma Albano J, et al.,* J Clin Oncol *(2002);16: pp. 3396–3403.*
28. *Osborne CK, Pippen J, Jones SE, et al.,* J Clin Oncol *(2002);20: pp. 3386–3395.*
29. *Howell A, Pippen J, Elledge RM, et al.,* Cancer *(2005);104: pp. 236–239.*
30. *Thürlimann B, Robertson JF, Nabholtz JM, et al.,* Eur J Cancer *(2003);39: pp. 2310–2317.*
31. *Lonning PE, Bajetta E, Murray R, et al.,* J Clin Oncol *(2000);18: pp. 2234–2244.*
32. *Bertelli G, Garrone O, Merlano M, et al.,* Oncology *(2005);69: 471–477.*
33. *Vergote I, Robertson JF, Kleeberg U, et al.,* Breast Cancer Res Treat *(2003);79: pp. 207–211.*
34. *Lewis JS, Meeke K, Osipo C, et al.,* J Natl Cancer Inst *(2005);97: pp. 1746–1759 .*
35. *Arimidex prescribing information, AstraZeneca Pharmaceuticals LP, Wilmington, Delaware, 2005.*
36. *Aromasin prescribing information, Pfizer Inc, New York, New York, October 2005.*