AROMATASE INHIBITORS IN BREAST CANCER: Spoiled for choice?

The range of aromatase inhibitors available and the differing indications for use and length of therapy may appear confusing to many who are not specialists in breast cancer. In the article below, Professor Alan Rodger, Medical Director, Specialist Oncology Services, from the Beatson Oncology Centre, describes their place in therapy. This is a shortened version of a very interesting and detailed review which can be found on our website.

A number of new treatments have recently been made available in the adjuvant management of early breast cancer. We now have three oral aromatase inhibitors (AIs) - letrozole, anastrozole and exemestane - to block peripheral (non-ovarian) post-menopausal oestrogen synthesis. Each is licensed for advanced breast cancer.

Is one better than the other? Probably not, and so far there is no head-to-head trial. As exemestane is steroidal, it may have a more profound inhibition of aromatase than the others. One study has shown that a further beneficial effect can be achieved in advanced disease in patients who have received and responded to non-steroidal AIs, relapsed and then been exposed to exemestane.

Several trials have researched the use of the different AIs in different adjuvant situations:

• Adjuvant use alone after appropriate local and other systemic cytotoxic treatment for 5 years in hormone receptor positive early breast cancer, ie as an alternative to tamoxifen.
The SMC has accepted anastrozole and letrozole for use in this situation.

• As a switch after 2½-3 years of tamoxifen to complete a total of 5 years of adjuvant hormonal therapy.
The SMC has accepted exemestane and anastrozole for use in this situation.

• As an extension, usually of 3 years, after 5 years of tamoxifen.
The SMC has accepted letrozole for use in this situation.

While these different schedules are confusing at first sight, there is scientific rationale. Trials show that in those three situations AIs produce statistically significant improvements in disease-free survival but, as yet, not in overall survival. Only one pre-specified subgroup (node positive) in one trial (extended letrozole after five years of tamoxifen) has so far shown a survival benefit.

So how do we decide which to use, if at all, and when? Until a head-to-head trial suggests otherwise (and one is being planned), each of these drugs is assumed to be equi-effective. They also seem to have the same toxicity range, though every clinician will know of a patient apparently intolerant to one but tolerant to another. Those toxicities differ from those found with tamoxifen. Studies suggest no overall difference in quality of life between AIs and tamoxifen.

PostScRxipt
from the
NHSGGC Area Drug & Therapeutics Committee
Issue 37 January 2007

In this issue . . .

Website
http://www.glasgowformulary.scot.nhs.uk

Side effect profiles

More common with AIs	More common with tamoxifen
Muscular and joint pains	Thrombo-embolic events
Osteoporosis/fractures	Endometrial cancer
Vaginal dryness, painful intercourse, loss of libido	Cold sweats
	Vaginal discharge

While, in the past, we have ignored the profound bone loss caused by premature menopause due to chemotherapy, oophorectomy or LHRH agonists, we are required to monitor it during AI use. The British Breast Group, in collaboration with osteoporosis research bodies, is developing useful evidence-based guidelines.

Taking account of toxicity, effectiveness, risk of recurrence and regulatory status, the West of Scotland Cancer Network's (WOSCAN) Breast Cancer Managed Care Network (MCN) has drawn up guidelines for the use of AIs.

Current WOSCAN guidelines for adjuvant use of aromatase inhibitors

• Very low risk Nottingham Prognostic Index (NPI) ≤3.4 and node negative	Tamoxifen alone for 5 years
• *ALL Her2+ • *ALL ER+ PR- • G3 or 4+ nodes, not having chemotherapy • Contra-indication to tamoxifen	Immediate anastrozole or letrozole for 5 years
• ALL G3 or 4+ nodes having chemotherapy • *Her2-, PR+	Switch to exemestane or anastrozole after 2.5 years of tamoxifen to complete 5 years
• The rest	Switch to letrozole for 3 years after 5 years of tamoxifen

**Using Her2 and PR status to guide use of AIs is not universally accepted as trial evidence is weak or contradictory.*

Anastrozole and letrozole are licensed and SMC-accepted for use over 5 years from initial treatment and in place

contd on page 4

Alphabetical list of most recent ADTC decisions

For full details of SMC advice, visit **www.scottishmedicines.org** For NICE advice, visit **www.nice.org.uk** For previous ADTC decisions, visit **www.glasgowformulary.scot.nhs.uk**

Drug	Indication under consideration (There may be other licensed indications)	Glasgow decision	
Adalimumab (Humira®)	Ankylosing spondylitis.	*Formulary.* Restricted to use in accordance with the British Society for Rheumatology (BSR) guidelines of July 2004.	✓R
Anastrozole (Arimidex®)	Adjuvant treatment of early breast cancer following 2-3 years of treatment with tamoxifen in postmenopausal women.	*Formulary.* Acknowledge new indication. Restricted to initiation by breast cancer specialists in accordance with Regional Cancer Advisory Group protocol.	✓R
Bisoprolol (ADTC Appeal)	Heart failure.	*Formulary*. The initiation and initial supervision of bisoprolol in confirmed cases of chronic cardiac failure is restricted to prescribers experienced in the treatment of heart failure in line with agreed protocols.	✓R
Dinoprostone (Propess®)	Initiation of cervical ripening at term (from 38th week of gestation).	*Formulary.* Acknowledge new formulation.	✓
Docetaxel (Taxotere®)	Hormone-refractory metastatic prostate cancer.	*Formulary.* Acknowledge new indication. Restricted to use by specialists in line with NICE Technology Appraisal 101 and Regional Cancer Advisory Group protocol.	✓R
Docetaxel (Taxotere®)	Metastatic gastric adenocarcinoma.	*Non-Formulary.*	x
Entecavir (Baraclude®)	Chronic Hepatitis B.	*Formulary.* Restricted to specialist initiation in line with Hepatitis MCN protocol.	✓R
Erlotinib (Tarceva®)	Locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.	*Formulary.* Restricted to use for those patients who would otherwise be eligible for treatment with docetaxel monotherapy.	✓R
Fludarabine (Fludara®)	B-cell chronic lymphocytic leukaemia.	Deferred for consultation with Regional Cancer Advisory Group.	?
Gemcitabine (Gemzar®)	Metastatic breast cancer.	Deferred for consultation with Regional Cancer Advisory Group.	?
Lanreotide (Somatuline® LA)	Thyrotrophic adenomas.	*Non-Formulary.*	x
Lopinavir/Ritonavir (Kaletra®)	Treatment of HIV-1 in adults and children >2 years.	*Formulary.* Acknowledge new formulation. Restricted to use by HIV specialists.	✓R
Methotrexate pre-filled syringes (Metoject®)	Rheumatoid arthritis.	*Formulary.* Acknowledge new formulation.	✓
Midazolam (ADTC Appeal)	Buccal use for prolonged seizures.	*Formulary.* Restricted to initiation by, or on the recommendation of, specialists in accordance with local protocol.	✓
Mitotane (Lysodren®)	Advanced adrenal cortical carcinoma.	*Non-Formulary.*	x
Natalizumab (Tysabri®)	Relapsing remitting multiple sclerosis.	*Non-Formulary.*	x
Oxycodone (Oxycontin®/Oxynorm®) (ADTC Appeal)	Post-operative pain.	*Non-Formulary.*	x
Pregabalin (Lyrica®)	Generalised anxiety disorder.	*Non-Formulary.*	x
Rasagiline (Azilect®)	Parkinson's disease (monotherapy).	*Non-Formulary.*	x
Rasagiline (Azilect®)	Parkinson's disease (adjunct therapy).	*Non-Formulary.*	x
Rituximab (MabThera®)	Rheumatoid arthritis.	Deferred to allow the development of a protocol by the Rheumatology Planning Group.	?
Rituximab (MabThera®)	Relapsed/refractory follicular lymphoma.	Deferred for consultation with Regional Cancer Advisory Group.	?
Solifenacin (Vesicare®) (ADTC Appeal)	Urge incontinence, urinary frequency, overactive bladder.	*Formulary.* Restricted to use in patients who fail to respond to, or tolerate, normal release oxybutynin.	✓R
Sorafenib (Nexavar®)	Renal cell carcinoma.	*Non-Formulary.*	x
Temozolomide (Temodal®)	Newly diagnosed glioblastoma multiforme.	Deferred for consultation with Regional Cancer Advisory Group.	?
Triptorelin (Decapeptyl® SR)	Precocious puberty.	*Formulary.* Acknowledge new indication.	✓

✓= *Formulary* ✓R = *Formulary* (restricted) **x** = *non-Formulary* **?** = awaiting final decision

Advice on medicines use from national bodies

Many people are confused by the different types of advice issued by national advisory bodies. We attempted to clarify some of the issues in *PostScript* 27, April 2005. NHS Quality Improvement Scotland (www.nhshealthquality.org) has recently issued a very useful summary of the different types of advice in their booklet *NHS QIS and NICE Advice: definitions and status*. The main issues relating to the work of the ADTC are shown below.

Advice type	Definition, remit and status in Scotland
SMC Advice	**Recommendations on all newly licensed medicines, new formulations of existing medicines and major new indications for established products incorporating cost effectiveness analysis.** NHS Boards are required to follow SMC recommendations. Unique drugs accepted for use by SMC should be made available uniformly within three months or within timeframes specified in national implementation plans. SMC review is mandatory for newly licensed medicines. ADTC determines local formulary status on receipt of SMC advice; not all 'accepted' drugs will be added to the *Formulary.* Consultation with the Prescribing Management Group is required for drugs with significant cost or service implications.
SIGN Guidelines	**Recommendations for effective practice to be taken into account when services are developed** for the management of clinical conditions where variations in practice are known to occur and where effective care may not be delivered uniformly throughout Scotland. When elements of SIGN guidelines are incorporated into NHS QIS 'essential' standards, they are obligatory. **SIGN does not undertake economic analysis.** It states that a number of approaches to the incorporation of resource issues into clinical guidelines are under development but none are regarded as sufficiently well proven or appropriate for use in the SIGN methodology. Guidelines may include commentary on the resource implications of recommendations if these are significant.
NICE Multiple Technology Appraisals (MTAs)	Recommendations on the use of new and existing medicines and treatments within the NHS in England and Wales. These usually follow some time after launch therefore may be an opportunity to consider further evidence than that reviewed by SMC. Can provide useful information on relative cost-effectiveness of drugs for the same condition although, confusingly, not all MTAs relate to more than one drug. A Scottish expert is usually involved in each NICE MTA, and a Scottish expert group of four or five review the draft appraisal. **For NHS QIS-validated MTAs, NHS Scotland should take account of the advice and evidence from NHS QIS and ensure that recommended drugs and treatment are made available to meet clinical need.**
NICE Single Technology Appraisals (STAs)	**SMC remains the main source of advice in Scotland for the use of newly licensed medicines.** However, the publication of NICE STAs will be monitored, and their impact assessed, by NHS QIS, SMC and SEHD. The status of NICE STAs will be reviewed after the first 15 NICE STAs are published.
NHS QIS Standards	Standards are statements of performance patients should expect from NHS Scotland and are applicable to all parts of NHS Scotland. 'Essential' standards are expected to be met wherever the service is provided; 'desirable' standards are recommended for NHS Scotland.
NICE Clinical Guidelines	**No formal status within Scotland** as SIGN has the responsibility to produce clinical guidelines for NHS Scotland. Recommendations on the appropriate treatment and care of people with specific diseases and conditions within the NHS in England and Wales. Some NICE clinical guidelines have been considered on an *ad hoc* basis. Unlike SIGN, NICE includes cost effectiveness analysis in all recommendations and undertakes a cost impact analysis for each guideline.
Other Clinical Guidelines	Guidelines developed by professional and other organisations (international, European and British) with recommendations for clinical practice. **No formal status** but may be influential in the management of conditions. Often have no economic assessment.

Aromatase inhibitors *contd from page 1*

of tamoxifen. Exemestane and anastrozole are licensed and SMC-accepted for use after 2.5 years of tamoxifen to complete 5 years. Which to use? My view, shared by several of the members of the NHSGGC Drugs in Oncology Group and being studied by Prescribing Management Group, is that we should consider choosing and promoting one of these as Drug of Choice. There seems no reason, in my view, why that should not be the cheaper.

Is that important? Well, yes. AIs cost far more than tamoxifen. We should explore, therefore, value for money. Tamoxifen 20mg/day for a year costs £29; AIs cost between £894 and £1,084 at standard dose. That is a possible increase of £1,055 per patient per year (3637%).

Summary

AIs are a fantastic addition to treating hormone sensitive post-menopausal breast cancer in the advanced setting; and they have made it possible to use more effective drugs in the adjuvant setting. Their toxicities are generally manageable and they are well-tolerated.

As there are, at present, three apparently equi-effective products, we can and should, when more than one is licensed for the same indication, consider 'Drug of Choice' recommendation. Protocols based on trial evidence and risk allows us to develop region-wide agreed policies that can be modified as trial data accumulate.

Finally, I commend to you a recent publication from Australia's National Breast Cancer Centre, *Recommendations for Aromatase Inhibitors as Adjuvant Endocrine Therapy*. It is written for clinicians and patients. It can be viewed at **www.nbcc.org.au** and is endorsed by the three relevant royal colleges in Australia.

Drug of Choice update: Triptorelin (Decapeptyl® SR)

Triptorelin 11.25mg (Decapeptyl SR) is the gonadorelin (GnRH) analogue of choice for metastatic prostate cancer. The Urological Cancer MCN and Drugs in Oncology Group endorsed this recommendation. For a full review of the evidence and a guide to preparing the injection, see *PostScript* Extra Number 8, June 2006 on our website.

There is no conclusive evidence that one GnRH analogue is more effective or has fewer adverse events than another for this indication. Decapeptyl SR may be more acceptable to patients as it is administered via a smaller needle than goserelin LA (21 gauge vs 14 gauge, respectively). It is also significantly less expensive than goserelin LA and leuprorelin 11.25mg.

All new patients with metastatic disease should be prescribed Decapeptyl SR if a GnRH analogue is appropriate. Existing patients with metastatic prostate cancer currently prescribed other GnRH analogues can be switched to Decapeptyl SR at the discretion of the prescribing physician without seeking advice from the initiating specialist. Goserelin should continue to be recommended for patients with locally advanced disease and those in adjuvant and neo-adjuvant settings.

For all article references, check our website http://www.glasgowformulary.scot.nhs.uk

New approaches to prescribing support

The Pharmacy and Prescribing Support Unit (PPSU) was established earlier this year to deliver NHSGGC's pharmaceutical and prescribing support services. It drew together staff from community pharmacy development, acute care, mental health pharmacy, pharmaceutical public health and prescribing support across Greater Glasgow and Clyde. Approximately 1,000 staff link with acute services, community health partnerships and mental health services.

The change to single system working, along with the introduction of the new community pharmacy contract, provides a unique opportunity to create a new approach to delivery of pharmaceutical care. The work focuses on patients and supporting other professionals who work with medicines, not on medicinal products themselves. PPSU's aim is to ensure that resources are harnessed within single system working to maximum effect, thus ensuring that medicines are used safely, effectively and efficiently for patient care.

The stakes are high; the projected expenditure for medicines in NHSGGC in 2006/07 is over £300m. A much wider group of professionals now has authority to prescribe medicines. This raises issues around risk management to avoid duplication or omissions in prescribing, but leads to more multi-disciplinary working and promotes better understanding among the professions.

The advisory committee structures such as Area Drug & Therapeutics Committee and the Prescribing Management Group have reviewed their structures and functions to take account of the new Board structures. Plans are in place to revamp the *Formulary*, taking the best of the different systems in Glasgow and Clyde to improve the usefulness of the document to all prescribers.

Although it is still early days, examples of the benefits for patients are emerging from this single system approach to providing pharmacy and prescribing support. Good practice is being shared among staff who have never worked together yet are geographical neighbours. Closer working between prescribers and PPSU staff embedded in the CH(C)Ps and directorates should ensure a more cohesive approach to medicines management and local ownership of prescribing initiatives.

NHS Greater Glasgow and Clyde

Area Drug & Therapeutics Committee
Chair: Professor M J Brodie

Communications Sub-group
Chair: Mrs A Thompson

Published by the Communications Sub-group to reflect the views of the Area Drug & Therapeutics Committee but not necessarily those of NHS Greater Glasgow and Clyde.

PostScRipt

PostScript Editor: Mrs A Thompson
Prescribing Team, NHS Greater Glasgow & Clyde
Pharmacy & Prescribing Support Unit
Queen's Park House, Victoria Infirmary, Langside Road
Glasgow G42 9TY Tel: 0141 201 5214 Fax: 0141 201 5338
E-mail: audrey.thompson@nhs.net

PostScript Web editor: Dr A Power

Design, layout and production control:
Strathcashel Publications Project Management (01505 850 344)
Printed by: Core Image, East Kilbride