Society for Endocrinology comments on the assessment report for the National Institute for Health and Clinical Excellence Appraisal of

Hormonal therapies for the adjuvant treatment of early breast cancer

Developed for the Society for Endocrinology by

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March 2006
This is a comprehensive report that attempts to summarise and evaluate data on 3 registered aromatase inhibitors in multiple trials with differing protocols and different patient populations. We recognise the impossibility of comparison of risk reduction across trials for these reasons and perhaps this should be stated more explicitly.

Although clinical benefit and cost-effectiveness data are presented this appraisal does not provide any formal guidance or treatment recommendations. We recognise the problems of carrying out such a difficult analysis but wish to make the following observations:

1. We concur with the overall conclusions drawn from some extensive clinical trials that aromatase inhibitors do provide valuable additional therapy for breast cancer and that the drugs provide cost-effective treatments.

2. We have some concerns that there are too many generalisations that suggest all aromatase inhibitors have common ‘class’ effects. This is a frequent error in considering so-called drug classes. Here, although all three drugs are, indeed, potent aromatase inhibitors they can not be described as having identical properties and so must be considered individually both in terms of efficacy and safety. For example, exemestane is a steroidal irreversible inhibitor whilst the azoles, letrozole and anastrozole are reversible inhibitors; letrozole has marginally greater intrinsic potency whilst letrozole shows greater selectivity; exemestane is said to preserve bone mass, perhaps because of androgenic activity of the drug or its metabolites whilst the azoles appear to cause some bone loss due to their marked induction of oestrogen withdrawal (1). Exemestane gives rise to steroidal metabolites that may stimulate proliferation of breast cancer cells and so limit its efficacy (2); this cannot occur with theazole aromatase inhibitors. Thus, we would urge very careful use of generalisations and greater emphasis on evidence from large well-controlled clinical trials.
3. Although neither of us has expertise in health economic models, it would have been helpful to understand better the characteristics and assumptions made and how well any model had been validated.

4. It is of some concern that none of the authors is a recognised authority in treatment of breast cancer and disappointing that one of us (MB), who was the original Principal Investigator of the ATAC trial received no communication from ScHARR during its deliberations. Furthermore, although Rob Coleman, a recognised breast cancer expert, was consulted about adverse events, no recognised breast cancer expert was involved in discussions about benefit. It is recognised that both Coleman and John Robertson, another internationally-distinguished breast cancer specialist were allowed to comment on the report but by that time the analysis was complete and conclusions made.

5. Relating to the analysis itself our first concern is that the importance of the biphasic hazard for relapse (Figure 1) is under-estimated. There happens to be a peak hazard for relapse at about two years after surgery. Furthermore about half the benefit of adjuvant anastrozole compared with tamoxifen is within this period.[3] As RFS is a good surrogate for breast cancer specific survival [4] we are unconvinced that the model really explores the trade-off between early reduction in recurrence and death that might be compensated for in the long run in the population as a whole. This would be scarce comfort for those developing recurrences in the first 48 months.

6. Our second and most major concern relates to the assumption in the model that the gains in the first five years will be lost in the next ten years. Even ScHARR concedes that the benefits maintained approach may not be unrealistic. The current assumption is not based on any evidence and in our view is implausible: there has never been a precedent for it.[4] If indeed, the assumption currently made is false there is an under-estimate of the true cost-effectiveness of aromatase inhibitors. We strongly urge, therefore that the model be used to re-calculate the cost-benefit using the assumption that gains in the first five years will be maintained so that a range of potential benefit can be displayed.
7. The efficacy-cost benefits are also diluted because the results are presented from the intention to treat population rather than the hormone receptor positive population who actually receive the drug and pay for it.

8. In projecting the numbers of breast cancers in the future we are unsure if sufficient regard is paid to the over-diagnosis of “pseudo-cancers” as a result of screening artefacts. ‘Tumours’ in such patients would have little chance of benefit from any adjuvant programme; so in effect the advances in the science of adjuvant endocrine therapy will be diluted when applied to “cancers” detected when trawling the ‘well’ population of women that would never have been a threat if left undetected. [5,6]

9. On the cost side of AIs, it is unclear whether account has been taken of the fact that in the ATAC trial the HR for hysterectomy was 0.25 in favour of anastrozole: this was for all gynaecological indications NOT just for endometrial cancer.

10. In the critique on QOL studies it was unclear whether any expert like Professor Lesley Fallowfield had been consulted because we do not accept the conclusions on the ATAC QOL study.

11. Finally although not part of the remit it would be interesting to compare this scholarly piece of work with the evidence adduced in favour of mammographic screening which in the opinion of MB is more PBM (politically-biased medicine) than EBM.

References:


by the 17-hydroxylated Metabolite of Exemestane in Breast and Endometrial Cancer Cells. Proc. AARC. 45, Orlando, FL., Abstract # LB-221 (Late-breaking Research section)


   http://press.psprings.co.uk/bmj/march/breastcancer.pdf

**Disclosures:**
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