

Meeting report

Aromatase 2004, Edinburgh, UK, 6–8 September 2004

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Abstract

Aromatase is the key enzyme involved in oestrogen biosynthesis. Oestrogens not only influence normal development and function but are also implicated in the aetiology and progression of many diseases. Over recent years rational drug design programmes have led to the development of agents that specifically and potently inhibit aromatase. The multidisciplinary international symposium Aromatase 2004 provided a forum in which basic scientists, translational researchers and practising clinicians reviewed latest results, exchanged opinions, and defined future needs for the regulation of oestrogen biosynthesis and the use of aromatase inhibitors.

Keywords: aromatase, breast cancer, hormone dependent disease, inhibitors, oestrogen biosynthesis

Introduction

Aromatase 2004 was held in Edinburgh, Scotland on 6–8 September 2004. More than 200 delegates and 30 invited speakers formed a faculty drawn from 23 countries. The programme embraced basic science, translational research and clinical practice. Topics included phenotypes of oestrogen deprivation and excess, regulation and role of aromatase, effects and end-points of aromatase inhibitors (AIs), AI use for breast cancer therapy and other clinical conditions, long-term effects, and resistance to AIs, from which the following perspective is distilled.

Phenotypes of oestrogen deprivation and excess

Two models of oestrogen insufficiency were described: aromatase knockout (ArKO) and estrogen receptor knockout (ERKO) mice.

The phenotype of ArKO mice, as described by Evan Simpson, included a metabolic syndrome with increased intra-abdominal adipose tissue accumulation, hyperinsulinaemia, hyperleptinaemia, decreased physical activity and decreased glucose utilization. Males developed striking sexually dimorphic hepatic steatosis and neuronal loss in some hypothalamic areas. This ArKO mouse

phenotype mirrored clinical features in a man with aromatase deficiency who developed type 2 diabetes, truncal obesity, acantosis nigricans and hepatic steatosis.

Describing the phenotype of ERKO mice, Ken Korach concentrated on the reproductive system and on hormonal carcinogenesis. He distinguished between mice knocked out for estrogen receptor (ER)- α and those knocked out for ER- β . Mammary gland morphology was severely disrupted in α ERKO females, whereas normal development occurred in the β ERKO mice. α ERKO mice were infertile, whereas β ERKO animals were subfertile. Additionally, ER- α appeared to be more influential in hormonal carcinogenesis than did ER- β .

Raj Tekmal studied the impact of oestrogen excess on mammary gland development in aromatase over-expressing transgenic mice. It was sufficient to induce neoplastic changes and may increase cancer incidence – effects abrogated by AIs.

Regulation of aromatase

The human aromatase gene (CYP19) is regulated by tissue specific promoters, and alternative splicing of the first exon provides tissue-specific regulation.

Control of aromatase in the breast was of particular interest. Enhanced oestrogen production in breast cancers could result from promoter switching induced by autocrine and paracrine factors. These mechanisms were discussed by Shiu-an Chen, who characterized transcription factors enhancing aromatase expression at promoters I.3 and II in breast cancers, and by Colin Clyne, who discussed the role of prostaglandin E₂ and liver receptor homologue-1 in the interaction between tumour and surrounding adipose tissue.

Describing novel mechanisms for regulation of aromatase transcription, Carole Mendelson emphasized the role of hypoxia in placental expression. The regulation of aromatase in brain, endometriosis/uterine fibroids and testis was reviewed by Nobuhiro Harada, Serdar Bulun and Serge Carreau. Bonnie King characterized macrophages in lavage fluid from breast ducts as being aromatase-positive by immunocytochemistry.

Investigational approaches

A new monoclonal antibody with which to measure aromatase immunohistochemically in breast cancer was described by Hiro Sasano. Standardization of both staining and scoring was emphasized. The most promising antibody (677) localized aromatase to different tissue components, but there were positive correlations between immunohistochemical staining of cancer cells and aromatase activity and mRNA expression.

The relative merits of models used to monitor the effects of AIs were reviewed by Angela Brodie. In the model of xenografts of MCF-7 cells (transfected with the aromatase gene) in nude mice, the combination of anastrozole and tamoxifen was no better than tamoxifen alone and inferior to single agent anastrozole in controlling tumour growth – an effect that was recently confirmed in the clinical setting. More recent results in this model suggest that addition of fulvestrant to letrozole may delay hormone resistance.

The effects and end-points of aromatase inhibitors

The endocrinology of the ‘third-generation’ AIs anastrozole, letrozole and exemestane was described by Jurgen Geisler in terms of effects on total aromatase inhibition and suppression of plasma oestrogen levels. All three compounds inhibited aromatase by 97–99% *in vivo* and suppressed the major circulating oestrogen in postmenopausal women, namely oestrone sulphate, by up to 99%.

Using neoadjuvant treatment protocols, Bill Miller showed that anastrozole, letrozole and exemestane produced marked molecular and pathological changes in ER-rich breast cancers. Changes in tumour morphology occurred in over 60%. Profound reduction in expression of a proliferation marker (MIB-1) and progesterone receptors

were seen in about 90%. Microarray RNA analysis subdivided tumours into distinct groups according to molecular changes, although the relationship to clinical/pathology response remains to be determined.

The clinical end-points used to establish disease efficacy in breast cancer trials were reviewed by Matt Ellis. He identified the need to develop more robust criteria to determine tumour response to therapy in individual patients and suggested that a combination of clinical, radiological, histopathology and multiple biomarkers be used.

A surgical perspective was provided by Mike Dixon. Results from neoadjuvant trials show that AIs have advantages in comparison with tamoxifen. More patients with locally advanced breast cancer become operable, more have breast conservation surgery with complete excision, and there are lower local recurrence rates.

Breast cancer therapy

Novel AIs are having a major impact on breast cancer therapy. Jim Ingle reviewed use in patients with advanced disease. Anastrozole and letrozole were superior to tamoxifen in the first-line setting, and in the second-line setting they were superior to megestrol acetate in terms of time to progression, overall response, clinical benefit and toxicity profile. (Exemestane exhibited a similar pattern over tamoxifen.) Although differences may exist between AIs, there are only limited trial results directly comparing the drugs in advanced disease, and there is no level 1 evidence to distinguish between them. Clinical trials are needed to determine optimal sequencing strategies and use of AIs in premenopausal women, either as monotherapy or in combination with suppression of ovarian function.

Nicholas Robert reviewed the three major trials in which AIs were given in the adjuvant setting for early stage breast cancer. In the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial, patients were randomly assigned to receive anastrozole or tamoxifen as initial therapy. In the IES (Intergroup Exemestane Study) trial, patients receiving tamoxifen for 2–3 years were randomly assigned to continue on tamoxifen or swap to exemestane. In the third trial, the MA17 trial, women receiving 5 years of tamoxifen were randomly assigned to receive letrozole or placebo. In all, AIs produced superior clinical results to the control arms. Important questions still need to be addressed. What is the optimal time to introduce AIs (initially or after 2–3 years or 5 years of treatment with tamoxifen)? What is the optimal duration of AIs? Is a particular AI superior in particular settings? Finally, how are patients best selected for treatment?

As discussed by Ian Smith, the primary clinical benefit of neoadjuvant therapy is down-sizing of the tumour. Evidence

of clinical response might also help in planning adjuvant management. Research benefits of neoadjuvant therapy in identifying mechanisms of response and resistance to treatment and associated predictive markers was emphasized. Two large clinical trials demonstrated that letrozole and anastrozole achieved higher rates of clinical response and conversion to breast conservation than did tamoxifen in large primary tumours; both AIs were more effective than tamoxifen against HER-2 positive cancers.

Clinical trials with AIs were summarized by Jack Cuzick. Third-generation inhibitors were at least as effective as tamoxifen in advanced disease and in the adjuvant setting, and had fewer side effects. Effects on new contralateral tumours were greater than those on recurrent diseases. Important results are expected from several trials due to report in the near future.

Robert Brueggeierner provided the evidence for co-regulating aromatase and cyclo-oxygenase as a therapeutic option for patients with hormone-dependent breast cancer. Details were given of an ongoing neoadjuvant trial of exemestane and celecoxib.

Per Lonning considered social economical issues. He concluded that clinical benefits of AIs in adjuvant therapy were achieved at acceptable cost. In the setting of prevention the appropriate calculations were complicated by difficulties in identifying high-risk groups; appropriate cost studies were deemed to be mandatory and to require careful consideration.

Premenopausal women

Effects and potential applications of AIs in premenopausal women were summarized by Dominique de Ziegler. AIs interfere with ovarian oestrogen production and elevate gonadotrophins. Consequently, follicular growth is stimulated in the ovary. AIs therefore offer an effective method for inducing ovulation and a treatment for infertility. Other applications in premenopausal women were for endometriosis and uterine fibroids, or even to achieve medical abortion.

Long-term effects of aromatase inhibitors

AIs are being considered as cancer preventatives and in other settings for which long-term administration would be necessary. It is therefore important that the effects of chronic administration are evaluated, but results from primary prevention trials are still awaited.

Tony Howell focused on 'vascular' events and cognitive function. He concluded that, to date, the third-generation AIs had no significant effects on cardiovascular, cerebrovascular and thromboembolic events; influences on cognitive function, although thought detrimental, were unassessable.

Effects on bone were reviewed by Richard Eastell. Data from large trials in breast cancer patients suggest that AIs may be associated with increased risk for fracture or osteoporosis. Comparisons have often been with tamoxifen, which itself may decrease bone turnover and change bone mineral density. Important questions remain unanswered. Is bone loss with AIs progressive? Are effects similar with all inhibitors? What are the risk factors for fractures? Can changes be prevented with agents such as bisphosphonates?

Long-term effects on the endometrium were considered by Sean Duffy. In general, AIs have a better gynaecological profile than tamoxifen. Results from the ATAC trial indicate that anastrozole suppresses the endometrium. Endometrial pathology including cancer was lower among patients receiving anastrozole and lower than expected rates in age-matched populations.

Resistance to aromatase inhibitors

Mitch Dowsett reviewed the mechanisms of resistance to AIs, which may be subdivided into *de novo*/intrinsic and acquired resistance. Absence of tumour ERs was a key marker of *de novo* resistance in breast cancer but, in ER-positive tumours, progesterone receptor negativity and over-expression of type I growth factor receptors were also influential. Acquired resistance could result from several mechanism, but hypersensitivity to oestrogen mediated through over-expression of other signalling systems, such as HER2, was highlighted.

In his plenary lecture, Richard Santen showed how crosstalk between ERs and growth factors through 'nongenomic' effects could lead to adaptive hypersensitivity and to resistance to AIs in oestrogen-deprived cells. Blocking key molecules on the pathways (mitogen-activated protein kinase, phosphatidylinositol-3 kinase and mammalian target of rapamycin [mTOR]) with agents such as farnesylthiosalicylic acid may extend the efficacy of AIs.

Stephen Johnston further considered the combination of endocrine agent with inhibitor of signal transduction. He presented the rationale for employing inhibitors of tyrosine kinase and farnasyl transduction and mTOR antagonists with AIs and pure anti-oestrogens. Randomized phase II/III clinical trials are in progress to test these strategies.

Kent Osborne also presented compelling results indicating that the combination of a variety of agents that inhibit epidermal growth factor receptor family signalling plus tamoxifen could completely abolish the growth of hormone sensitive tumours. He confirmed that AIs were effective in blocking ER genomic and nongenomic pathways, and that growth factor pathways contributed to resistance to AIs. The plea was made for future clinical trials to be accompanied by molecular profiling.

Conclusion

The explosion of activity surrounding aromatase and its inhibitors was reflected in the presentations at Aromatase 2004. It was clear that, although many issues had been resolved, many questions remained to be answered. These will be challenges for the next Aromatase Symposium, which will be held in the USA in 2006.

Competing interests

The author(s) declare that they have no competing interests.