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Short Abstracts

Abstract 1

RATIONALE FOR A STUDY TESTING AROMATASE INHIBITORS IN PREVENTION AND DCIS

J. Cuzick

The rationale for using aromatase inhibitors for women with ductal carcinoma *in situ* (DCIS) or at high risk of developing breast cancer will be presented. When DCIS is treated by breast-conserving surgery, adjuvant therapies are aimed at both local control and the prevention of new contralateral tumours, whereas for women treated by unilateral mastectomy the only issue is the development of new tumours. This rate is typically at least as high as that required for entry into prevention trials. Aromatase inhibitors offer the potential for prevention that is likely to be at least as good as for tamoxifen, but with a lower-side effect profile. The increased risks of endometrial cancer and thromoboembolic disease found with tamoxifen should be eliminated, but fractures may be an important new side-effect. These may or may not be controllable with bisphosphonates or vitamin D and calcium supplements. Data from the advanced disease trials using aromatase inhibitors will be reviewed. Key data will come from the large Arimidex, Tamoxifen, Alone or in Comberation (ATAC) adjuvant trial.

Abstract 2

THE LATEST ON ER-β IN BREAST CANCER

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In order to evaluate the clinical relevance of measuring ERß along with ERα in breast cancer, *52* frozen and 24 fixed archival breast samples were re-examined for statement of the two oestrogen receptors. Most of the epithelial cells of normal and fibrocystic breasts expressed ERβ but ERα was rare. ERß-containing cells were abundant in ductal and medullary cancer and those containing ERα in ductal and lobular cancer. The percentage of Ki67-positive cells in the cancers varied between 0.1 and 33.5%. In none of the samples was ERα colocalised with Ki67, while in most Ki67-positive cells Erß was coexpressed. Samples which were ERα (−) ERß (+) had a significantly higher population of cells expressing both Ki67 and cyclin A than other samples In some samples, ERßcx, the ERß isoform which does not bind oestradiol, but which silences ERα was detected by reverse transcriptase-polymerase chain reaction (RT-PCR). The presence of this isoform could result in oestrogen resistance in ER-positive cancers. Since the response of breast cancers to tamoxifen is correlated with the presence of ERα, the population of cells containing ERß and Ki67 represents a novel population of proliferating cells which are at present not targeted by antioestrogens. We therefore examined another group of patients who were treated with tamoxifen for their breast cancer and who relapsed during or after the treatment. In order to evaluate the clinical relevance of ERß in breast cancer, 34 fixed archived primary breast samples were re-examined for both ERα and ERß, as well as proliferation markers, Ki67 and cyclin A. Six of these samples were from women who developed recurrent breast cancer after tamoxifen treatment and these sections permitted a comparison of the primary and recurrent cancer. In recurrent cancer, ERα, ERß and Ki67 were clearly more highly expressed than in the primary cancers. Like the primary cancers, many ERβ-containing, but very few ERα-containing cells expressed Ki67 and cyclin A. Surprisingly, ERß, but not ERα was expressed in stromal cells of all samples. All of these projects are ongoing and will provide insight into how manipulation of ERß function can be used in the therapy of human diseases. Thus, appropriate ER-β-specific ligands, perhaps in combination with tamoxifen, maybe useful in improving the treatment of breast cancers.

Abstract 3

THE ATAC-TRIAL

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The ATAC trial investigates the role of anastrazole (Arimidex), a third generation aromatase inhibitor, as an adjuvant treatment for post-menopausal women with hormone sensitive breast cancer. The rationale for this study was the finding of a better time to progression

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and overall response rate for anastrazole when compared with tamoxifen in women with oestrogen receptor-positive advanced breast cancer. There was also a significant difference in thrombo-embolic events in favour of anastrazole.

The trial recruited postmenopausal women with breast cancer who had completed primary therapy (including chemotherapy, if indicated). Patients were randomised to one milligram of anastrazole with a tamoxifen placebo or 20 m tamoxifen and an anastrazole placebo or the combination of both active agents. The trial was powered to show superiority of one arm after 1760 events.

Over 9300 women were entered from 380 centres making this the largest adjuvant breast trial ever. Four sub-protocols were designed; these included pharmacokinetics (357 patients), endometrial side-effects (285), bone safety (305) and quality of life (1105). The study end points include relapse-free survival, safety, time to distant recurrence, time to death and incidence of contralateral primary disease. Interesting differences in the mastectomy rate between different countries has emerged with a higher than expected mastectomy rate for T 1 tumours.

The results of the first analysis will not be available until December 2001, but there are various scenarios that might be considered. These include (1) no significant difference between any of the three arms, but a beneficial side-effect profile for anastrazole or the combination. (2) A small, but significant, benefit for anastrazole over tamoxifen or the combination with or without a beneficial side-effect. (3) A small, but significant, benefit for anastrazole or the combination over tamoxifen with or without beneficial side-effects. It is unlikely that tamoxifen alone will prove superior.

There is emerging evidence that the third generation aromatase inhibitors are more potent than tamoxifen in achieving the response when used in the neo-adjuvant setting and if this is translated into the adjuvant setting then we may well see a benefit.

Abstract 4

LESS FAVOURABLE CLINICOPATHOLOGICAL CHARACTERISTICS OF ENDOMETRIAL CANCERS AFTER TAMOXIFEN USE

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Conclusive evidence has emerged that tamoxifen is associated with a moderately increased risk of endometrial cancer. An important question is, however, whether the clinicopathological characteristics and ultimate prognosis of endometrial cancers following tamoxifen treatment are different from those in patients not treated with tamoxifen. In four small early studies, the stage distribution and histological features of endometrial cancers in tamoxifen-treated women were not remarkably different from those diagnosed in non-treated women. Magriples and colleagues, however, reported a higher frequency of poorly differentiated and high-grade tumours with a poor prognosis in tamoxifen-treated patients. In the Dutch study, which included 309 patients with endometrial cancer following breast cancer, endometrial tumours with FIGO stage III and IV occurred more frequently among long-term tamoxifen users (2 or more years) than in non-users (17 versus 5%, $P = 0.006$). Based on a centralised review of diagnostic pathology slides, long-term tamoxifen users more often developed malignant mixed mesodermal tumours or sarcomas of the endometnum than did non-users (15 versus 3%, $P = 0.02$). Furthermore, the tumours diagnosed among long-term tamoxifen users were more often p53-positive and oestrogen receptor-negative and specific *TP53* mutations were found. In addition, the 3-year actuarial endometrial cancer-specific survival in this study was significantly worse for long-term tamoxifen users than for non-users, largely due to the less favourable tumour characteristics associated with tamoxifen use. The Dutch findings have recently been confirmed in several other series and the total available literature will be reviewed.

Abstract 5

LOCAL PROGESTINS TO COUNTERACT TAMOXIFEN AND OESTROGEN'S ENDOMETRIAL EFFECT

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Tamoxifen, a non-steroidal triphenylethylene compound, is currently the endocrine therapy of choice for all stages of breast cancer, and a course of treatment for more than 2 years is more effective than a shorter course. The degree of inhibition or activation of oestrogen receptor genes varies between different tissues. Indeed, it exerts oestrogenic actions on bone turnover, parts of lipids metabolism, and on the endometrium.

Tamoxifen exerts on the endometrium other, non-classical oestrogenic, effects. There is an increase incidence of endometrial polyps in tamoxifen users and this may be the source of uterine bleeding, but these polyps are asymptomatic in the main. Endometrial hyperplasia and carcinoma occur at a higher rate in tamoxifen-treated women. As it is assumed that the endometrial effect of tamoxifen treatment is the result of its oestrogenic effect, our hypothesis was based on rendering the endometrium unresponsive by continuously administered

progestogen. A randomised trial of endometrial surveillance with or without levonorgestrel (LNG)-IUD (intra-uterine device) for one year, was conducted. Of the 113 women enrolled into the study, 47 women in the LNG-IDS group, and 52 controls, completed one year of observation. The induction of decidual endometrium was confirmed in 40 women treated with LNG-IDS. The incidence of polyps did not change, but 13% fewer fibroids were detected at hysteroscopy.

Endometrial screening of asymptomatic tamoxifen users is accepted and well tolerated by these women. Conclusions to be derived from this study include the feasibility of antagonising the proliferative effects of tamoxifen by fitting these women with LNG-IDS with the induction of decidual changes. Whether long-term use of this treatment will effectively reduce tamoxifen-related uterine pathology remains to be confirmed.

Abstract 6

THE ARIMIDEX, ALONE OR IN COMBINATION (ATAC) ADJUVANT BREAST CANCER TRIAL: BASELINE ENDOMETRIAL SUB-PROTOCOL DATA

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On behalf of the ATAC Trialists Group (Endometrial sub-protocol)

1. Introduction

The ATAC trial is a randomised double-blind trial comparing anastrazole (Arimidex) alone or in combination with tamoxifen relative to tamoxifen alone as 5 year adjuvant therapy for postmenopausal women with early breast cancer. Since tamoxifen is associated with endometrial changes, the ATAC Endometrial Sub-Protocol was initiated to evaluate prospectively the incidence and nature of subsequent intra-uterine changes following endocrine therapy.

2. Methods

Random double-blind allocation to three arms 1:1:1 to anastrozole 1 mg, tamoxifen 20 mg or a combination of both. Baseline assessment by hysteroscopy and ultrasound were carried out. Follow-up was undertaken at 1, 2 and 5 years post-treatment. All patient were postmenopausal with an intact uterus.

3. Results

The main trial recruited over 9300 patients, 285 of which entered the Endometrial SubProtocol. The findings at hysteroscopy, ultrasound and pipelle biopsy at baseline will be presented. This dataset represents a unique insight into the uterine findings in an asymptomatic cohort of postmenopausal women.

Abstract 7

EURALOX 1: UTERINE SAFETY OF KILOGEST VERSUS EVISTA: PRELIMINARY RESULTS

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For the Euralox 1 Study Group

1. Background

Raloxifene, a selective oestrogen receptor modulator (SERM), is indicated for the prevention and treatment of postmenopausal osteoporosis. This multicentre, randomised double-blind trial compared the uterine effects of raloxifene with a continuous combined hormone replacement therapy (cc HRT), a preparation of 2 mg 17ß-oestradiol (E2) and 1 mg norethisterone acetate (NETA) for a duration of 6 or 12 months.

2. Methods

1008 asymptomatic postmenopausal women with an endometrial thickness of less than 5 mm were randomly assigned to receive raloxifene or ccHRT for 6 months. A subset was randomised for 12 months. The frequency of vaginal spotting/bleeding was recorded in a diary each participant carefully kept throughout the study. Endometrial thickness and uterine volume were measured by transvaginal ultrasonography (TVU) at baseline and after 6 months in the study according to a gynaecological surveillance algorithm (Fig. 1). The average number of days per month a patient was bleeding/spotting was expressed in a graphical manner (Fig. 2). The different numbers in this figure refers to the number of women remaining in the study per treatment group, starting with 1003 patients with 855 still in the trial at the 6 month follow-up.

3. Findings

After six months of therapy, a total of 6.8% of all women on raloxifene reported vaginal bleeding and spotting compared with 55.1% in the ccHRT group. Raloxifene treatment was not associated with a significant change from baseline to endpoint in mean endometrial thickness ($P=0.107$), whereas ccHRT treatment was associated with an increase in this value of (mean +/−standard deviation (SD)) 1.17 +/− 2.18 mm ($P<0.001$). At endpoint, mean endometrial thickness was significantly higher in the ccHRT group (4.56 +/− 2.l4 mm; change from baseline $P<0.001$), compared with the raloxifene group (3.47 +/− 1.66 mm;

change from baseline $P=0.107$). In the raloxifene group, there was a trend towards a decrease from baseline in uterine volume (from 31.37 +/− 20.28 to 30.32 +/− 16.21 mm; $P=0.369$); in the ccHRT group there was a significant increase in uterine volume (from 31.27 +/− 16.32 to 54.04 +/− 36.12 mm; $P<0.001$), and the difference in the effect of both compounds on uterine volume at endpoint reached statistical significance ($P<0.001$). Preliminary results of the 12 months follow-up data will also be presented.

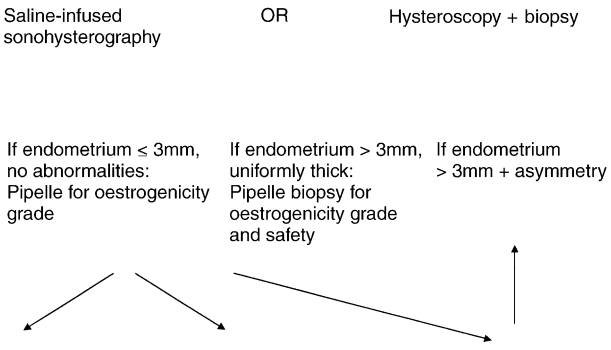

Fig. 1. Gynaecological surveillance algorithm used in the Euralox 1 study. In patients who underwent a routine Pipelle biopsy at baseline (group A), this algorithm was administered in cases of repeated bleeding/spotting at the 6-month visit (visit 4) if the routine TVU showed an endometrial thickness of >5 mm. In patients without routine Pipelle biopsy at baseline (group B) who had repeated bleeding/spotting during the study, the algorithm was administered at visit 3 or 4 as needed.

4. Interpretation

Unlike ccHRT, six months of raloxifene treatment does not lead to vaginal bleeding/spotting and is not associated with increased endometrial thickness or uterine volume (Figs. 1 and 2).

Abstract 8

PROGESTOGENS: PROOF FOR ENDOMETRIAL PROTECTION IN LONG-TERM OESTROGEN USERS?

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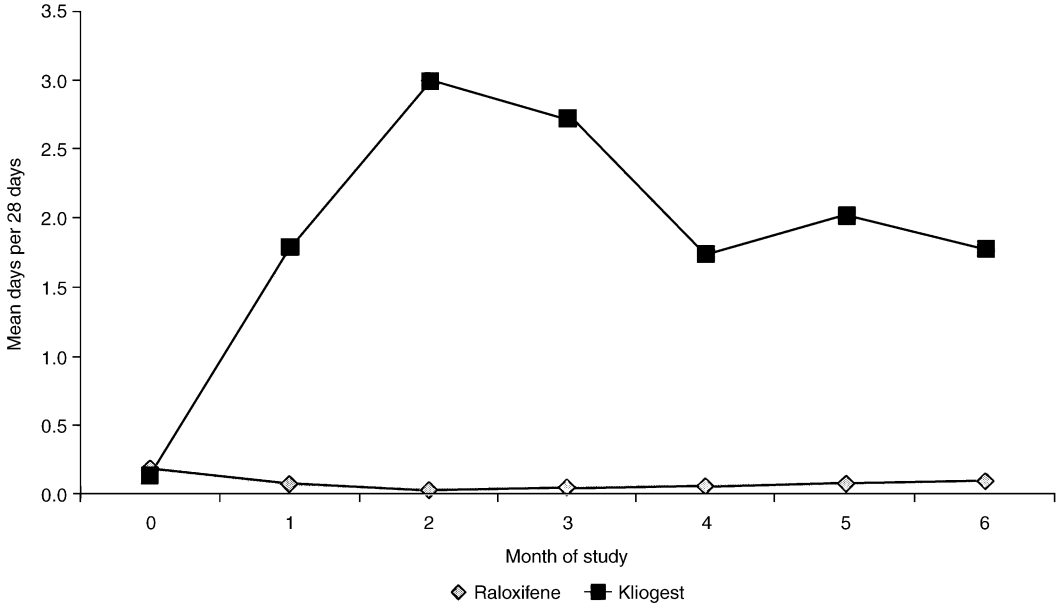
Evidence that the use of oestrogens unopposed by a progestogen increased the risk of endometrial carcinoma emerged during the middle 1970s. Within 5 years, it had been established that the increase in risk of endometrial cancer in postmenopausal oestrogen users was both dose- and duration-dependent. By the late 1970s, histological, biochemical and ultrastructural studies had demonstrated that the sequential edition of a progestogen to the oestrogen reduced the risk of the development of endometrial hyperplasia. The protective effects of progestogen were, again, both dose- and duration-dependent.

Epidemiological studies showing that either cyclical (3 weeks out of every 4) oestrogen or continuous oestrogen (for 365 days each year) with sequential progestogen did not increase the risk of endometrial cancer became available in the early 1980s. However, many of these studies had observed therapy when given for relatively



Raloxifene *n*=492	480	477	474	454	449	447
Kliogest *n*=511	494	479	457	420	416	408

Fig. 2. Mean bleeding rate in Euralox 1 subjects by month of study (in days per month).

short periods of time (up to 5 years). More recent epidemiological investigations, largely, from the West Coast of the USA, have confirmed that the protective action of progestogens on risk of endometrial cancer is dependent on the duration of progestogen each month. However, these studies have also suggested that with extended durations of use of Hormone Replacement Therapy (perhaps 10 years) then the relative risk of the development of endometrial cancer begins to rise. The increase in risk has been observed in women taking unopposed oestrogen therapy before changing to a sequential oestrogen/progestogen regimen, and has also been observed in women taking progestogen for 9 or fewer days each calendar month. However, even durations of progestogen each month of more than 10 days have been associated with a doubling in the risk of endometrial cancer with very long-term use.

During the last 10 years, there has been a major change in the prescribing of HRT in most of Europe. This is because of the introduction of continuous/combined oestrogen/progestogen regimens which have the aim of achieving amenorrhoea and thereby obviating the regular withdrawal bleed. Short-term studies (1–2 years) of such treatments have shown effective suppression of endometrial hyperplasia: gonadomimmetic treatments may behave likewise. It is probable that these newer treatments will be more protective in the very long-term against the development of endometrial cancer, but confirmatory data from appropriate epidemiological investigations are awaited.

Abstract 9

HORMONE REPLACEMENT THERAPY IN BREAST/ENDOMETRIAL CANCER SURVIVORS

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Sex steroid-related tumours in women are represented by breast and endometrial cancers. A possible relationship exists between sex steroids and both ovarian and colon cancer. Sex steroids do not damage DNA directly. They stimulate or inhibit epithelial **cell proliferation**, and thus can modulate tumour growth, developmental progression, invasion and metastasis ability.

Among current oestrogen replacement therapy (ERT) users (or those who stopped use 1–4 years previously), the relative risk of having breast cancer diagnosed increases by a factor of 1.02 for each year of hormone use. This effect is largely limited to lean women. The breast cancers diagnosed during ERT are more likely to contain ER and are less aggressive. Some reports indicate no increase or even a decrease in breast cancer mortality in hormone replacement therapy (HRT) users. An oestrogen-progestin regimen may increase breast cancer risk beyond that associated with oestrogen alone. However, the effect of progestogens on the breast awaits further clarification.

ERT/HRT is generally considered to be contraindicated in breast cancer patients, as no firm data are as yet available from randomised clinical trials. ERT/HRT could, however, be considered for breast cancer patients suffering from menopausal symptoms resistant to alternative treatments, particularly in women with ER-(hormone-resistant) cancers.

Unopposed oestrogen therapy is known to increase the endometrial cancer risk, and is appropriate only for hysterectomised women. To negate the excess risk of endometrial hyperstimulation, an adequate progestin dose must be given in a continuous combined regimen or for an appropriate number of days in sequential regimens (10 days or more for some progestogens or 12 days or more for other progestogens).

An appropriate combination of oestrogen and progestin does not appear to increase, and may even decrease, the risk of endometrial cancer. HRT is generally considered to be contraindicated in endometrial cancer patients. Despite the potential risks, HRT could be considered for patients suffering from menopausal symptoms resistant to alternative treatments, after completely informed consent is given.

Circumstantial evidence suggests a reduced risk of colorectal adenoma and colon cancer in current users of HRT, but definitive studies are mandatory. There is no contraindication to HRT prescription in colon cancer survivors. Consistent epidemiological data describe a decreased incidence of ovarian cancer with oral contraceptive use during the reproductive years. Studies on HRT and risk of epithelial ovarian cancer have produced conflicting results, but most data seem to exclude a strong association. While no data contraindicate HRT use in epithelial ovarian cancer survivors, current studies do not allow us to exclude the possibility that oestrogens and Selective Oestrogen Receptor Modulators (SERMs) alone could stimulate ovarian cancer growth in a small fraction of patients. Additional studies are required.

It is important to consider that not all oestrogens and progestins are used at the same dosage, route of administration (oral, transdermal and for oestradiol intranasal) and, mostly, different oestrogens do not show the same bioavailability and tissue effects. The available data do not allow us to discriminate for all these variables and therefore it is inappropriate to consider jointly all forms of hormonal therapy. This issue is considered as an important area for future evaluation and research.

Abstract 10

PREVENTION OF BREAST CANCER

J. Cuzick

Breast cancer is only partially controlled by treatment and screening, and new approaches are needed if a

major impact on the public health burden of this disease is to be achieved. The most appropriate method of prevention depends on the degree of risk, and interventions need to be tailored specifically to the women's risk profile. For normal risk women, weight control, exercise and possibly alcohol modification are the only sensible prevention strategies, in addition to screening which does not prevent disease, but can lower mortality. As risk increases, more intensive interventions can be considered, including various chemopreventive strategies and, for very high-risk women, surgical measures such as oophorectomy or bilateral mastectomy. These various approaches will be surveyed and current activities reviewed.

Abstract 11

WHICH ADJUVANT ENDOCRINE THERAPY FOR ER-POSITIVE NON-METASTATIC BREAST CANCER? EBCTCG-2000 UPDATE: TAMOXIFEN, CASTRATION, LHRH-AGONISTS

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In early breast cancer, all clinically apparent disease can be removed surgically. Following such surgery, adjuvent systemic treatments involving various cytotoxic, hormonal or other therapies may be considered. Before the 1980s, despite many trials of different adjuvent therapies, there was substantial uncertainty as to the net effects of such treatments, particulary on survival, because none of the trials individually was large enough to provide reliable answers. In 1983–1985, the Clinical Trial Service Unit (CTSU) established the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) to bring together updated data on each woman randomised into all trials of the treatment of early breast cancer, in an ''overview'', or series of systematic reviews. These meta-analyses provide definitive evidence on the effects of treatments on recurrence, second cancer and mortality, which could not be obtained by other means. The fourth cycle of data collection (involving 200,000 women in over 300 randomized trials, done by 250 trial groups) was presented to the EBCTCG for discussion in September 2000. In the trials of adjuvant hormonal therapy, analyses were available for 10,000 in trials of ovarian ablation or suppression and 80,000 in trials of tamoxifen (50,000 in trials of tamoxifen versus control, and 30,000 in trials of different durations of tamoxifen). The main results will be presented.

Abstract 12

CLINICAL IMPLICATIONS OF NEW SERMS

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Recent advances in our understanding of the field of oestrogen action and its modification by small molecules and proteins has created great excitement in the scientific and clinical community dedicated to women's health care. Over the last few years, the introduction of new ''designer oestrogen'' compounds into clinical practice and clinical research has simulated our interest in the areas of hormone-dependent cancers and the global actions of oestrogen in women. A growing understanding of dietary and environmental oestrogens such as the phytooestrogens has also stimulated new interest in the cellular and pharmacodynamic consequences of oestrogen receptor-mediated agents. In addition to their role as preventives or therapeutics for hormone-dependent cancers, these new agents, to be successful, must have utility in mimicking the use of oestrogen in maintaining bone and cardiovascular health. Side-effect profiles and additional, non-oncological clinical uses may prove important in determining which of the newer agents are successful as widely used clinical agents. It is important as these new drugs and new drug classes are introduced into the clinic, therefore, that we understand the consequences of their use for the long-term health of women, as well as the similarities and differences which could impact upon their use as agents for benign and malignant human disease.