Friday, February 27, 1998 9.00–18.00

Adjuvant Endocrine Therapies

P96 Randomized trials to assess the effectivity of tamoxifen as adjuvant treatment in node-negative and receptor positive breast cancer. The Heidelberg II and GABG II trials

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Goal: To assess the effectivity of a 2 years treatment of tamoxifen (30 mg/day) in patients with oestrogen- and/or progesterone receptor (ER, PR) positive primary breast cancer (pT1-3, pN0, M0).

Patients and Methods: Between 1979 and 1990 713 patients have been randomized to be either treated with tamoxifen or to be observed only. 73 (10.2) patients had to be excluded for various violations of eligibility criteria, so that 325 patients with tamoxifen therapy and 315 patients as a control group could be evaluated in this per protocol analysis. As pre- and postmenopausal patients were recruited, median age at diagnosis was 62 years (range 32–90). 93.1% of the patients had either ER and or PR positive tumors (≥10 fmol/mg), in 6.9% the receptor status was unkown. Median follow up is now 69 months (range 3–217); 156 patients have died during the observation period.

Results: Clinical outcome of the patients was dependent on age and ER content. Patient older than 70 years and patients with an ER content of >100 fmol/mg showed a significant better outcome ($p = 0.008$ and $p = 0.03$). Tumor size and PR content were not predicitve. In contrast to our first analysis in 1994 we can now observe a trend for a better outcome in patients with tamoxifen treatment (local disease free-survival, LDFS, $p = 0.3$, distant disease free survival, DDFS, $p = 0.04$; overall survival, OS, $p = 0.3$). This trend is more obvious for patients with ER >100 fmol/mg (LDFS: $p = 0.03$, DDFS: $p = 0.01$ and OS $p = 0.07$). Effectivity seems to be slightly less dependent on PR status (more or less than 100 fmol/mg) LDFS: 0.3; DDFS: $p = 0.07$ and OS: $p = 0.07$).

Conclusion: Oestrogen receptor content is predictive for the effectivity of adjuvant tamoxifen therapy in low risk patients with primary breast cancer.

P97 Endometrial cancer and endometrial hyperplasia in postmenopausal women with breast cancer

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Introduction: There is a higher incidence of endometrial cancer in postmenopausal women with breast cancer who receive tamoxifen in the adjuvant setting. The question is discussed whether those second carcinomas are caused by the partial estrogenic acting of the tamoxifen or if tamoxifen leads to an earlier clinical manifestation of preexisting 'second primaries' or praecancerosis.

Materials and Methods: To evaluate the incidence of preexisting endometrial lesions in postmenopausal women with breast cancer we initiated a prospective non randomized study. During a 18 months period a total of 68 potential candidates were seen, 31 of whom, however, had been hysterectomized. After given informed consent and preoperative transvaginal B-mode ultrasound examination with color-flow-mapping a D&C was performed in the remaining 37 postmenopausal women (age 63.7 ± 9.9 years) with intraoperatively confirmed breast cancer during the same procedure.

Results: 28 women out of these 37 received tamoxifen and nine were not receiving tamoxifen in the adjuvant setting. Those who did not receive tamoxifen had normal histological findings of the endometrium. But of the 28 patients who received tamoxifen 12 had a normal endometrial histology, one had an adenomatous hyperplasia and two had endometrial cancer – these three were operated on adequately before receiving tamoxifen.

Conclusion: Despite the small number of patients our data seem to support the theory that postmenopausal women with breast cancer have preexisting endometrial lesions that may earlier become symptomatic if tamoxifen is used in an adjuvant setting. As both patients with endometrial cancer had abnormal ultrasound findings at least a qualified transvaginal B-mode ultrasound of the endometrium is neccessary before a breast cancer in postmenopausal women will be operated on. The indication for an intraoperative endometrial biopsy has to be discussed.

P98 Preliminary report; Zoladex and tamoxifen as adjuvant treatment in premenopausal breast cancer

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A randomised clinical trial, using an essentially common protocol was initiated by four cancer trial groups in the late 1980's. The purpose was to evaluate the effects of tamoxifen and Zoladex (a luteinising hormone-releasing hormone agonist) in women under 50 with operable breast cancer, irrespective of nodal status, on survival and disease-free survival. A 2 × 2 factorial design was employed. After primary therapy (surgery with or without local irradiation and/or chemotherapy) patients were randomised to control, tamoxifen (20 mg orally o.d. for 2 years), Zoladex (26 monthly injections) or combination. Alternatively, patients electively received tamoxifen or not, and were randomised just for Zoladex.

By the end of September 1997, 1,128 patients had entered the trial in the UK and the other three groups had collected a similar total. Preliminary analysis of the UK data in October 1996 on patients entered up to 31st Dec 1995 (n = 971), showed that 59% were node negative, 27% node positive and 14% were of unknown nodal status. The oestrogen receptor (ER) status was positive for 16% patients, negative for 10% but unknown for the majority (74%). Local excision was carried out in 554 (57%) patients, mastectomy in 417 (43%) and chemotherapy was given in 340 (35%). Nodal status, ER status, type of surgery and numbers treated with chemotherapy were equally balanced between Zoladex and non-Zoladex treatment groups. The total number of first events was 179 and of deaths was 95.

The outcome data are to be analysed in November and will be presented at the meeting.

P99 Arimidex, tamoxifen alone or in combination (ATAC) adjuvant trial in post-menopausal breast cancer

M. Baum, J. Houghton. *On behalf of the ATAC Steering Committee, UK*

Tamoxifen is currently the agent of choice as adjuvant endocrine therapy for early breast cancer. Notwithstanding the effectiveness of tamoxifen, particularly in the post-menopausal patient, it is important to evaluate alternative endocrine therapeutic agents in this patient population. Anastrozole (Arimidex™) is a selective oral aromatase inhibitor which has proven efficacy in advanced breast cancer (1), and because of its good tolerability, and a mechanism of action distinct from tamoxifen, Arimidex is to be evaluated as an alternative endocrine therapeutic agent in post-menopausal women with early breast cancer. It is considered that the benefits of Arimidex either alone or in combination with tamoxifen could include improved efficacy, and the possibility of a reduction in the side effects associated with the partial agonist effects of tamoxifen.

The ATAC trial has been designed to compare the efficacy and safety of tamoxifen alone, with Arimidex alone, and with the combination of tamoxifen plus Arimidex, as adjuvant treatment in post-menopausal women with early breast cancer, who have completed their primary therapy. Treatment will be for 5 years or until first recurrence using the most widely prescribed dose of tamoxifen (20 mgs od) and the registered dose of Arimidex (1 mg od).

The main study endpoints are: time to recurrence of breast cancer, overall survival, safety and tolerability. To be included in the trial, patients must be post-menopausal, have histologically proven operable breast cancer, have completed all primary surgery and/or radiotherapy and chemotherapy (if given), and also be candidates for adjuvant hormonal therapy. This study is now enrolling patients with good recruitment.

In addition to the main study, there are also five sub-protocols each designed to allow important comparison between Arimidex and tamoxifen. These include 1) Quality of life, where data will be collected on patients in each of the three treatment arms; 2) bone mineral density and bone resorption and formation; 3) evaluation of the incidence of abnormal endometrial histology; 4) profiling lipids in a sub-set of patients, and 5) evaluation of the plasma levels of the drugs in combination compared to the two drugs alone. The status of the trial and sub-protocols will be updated.

Arimidex is a trademark property of Zeneca Limited

[1] Buzdar A et al. Proc. ASCO 1997; 16, 156a, Abstr 545.

P100 'Arimidex' (anastrozole): Lack of interactions with tamoxifen, antipyrine, cimetidine and warfarin

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'Arimidex' (anastrozole), a potent, oral, once daily, selective non-steroidal aromatase inhibitor is currently under study versus tamoxifen and the combination of 'Arimidex' plus tamoxifen, as adjuvant therapy of breast cancer in postmenopausal women (ATAC). Results from in vitro studies have predicted a