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

lack of interactions between anastrozole and other drugs metabolized by cytochrome P450 enzymes (1). We report on four clinical trials which showed that anastrozole did not interact with tamoxifen, antipyrine, cimetidine or warfarin.

The effect of anastrozole on tamoxifen pharmacokinetics (PK) was assessed in a randomized, double-blind, placebo-controlled trial involving 34 post-menopausal women with early breast cancer, who were already receiving tamoxifen (20 mg daily) as adjuvant therapy. These patients were randomised to also receive either anastrozole or placebo. Randomised therapy was given for 28 days from Day 0. There was no evidence of anastrozole having any significant effect on the blood levels of tamoxifen compared to placebo ($p = 0.919$). As expected, the oestradiol levels were significantly lower in the group of patients that received anastrozole than those receiving placebo ($p < 0.001$). Suppression of oestradiol levels in the combination group, was consistent with that seen in studies of patients treated with anastrozole alone.

The effect of anastrozole on warfarin PK/pharmacodynamics was assessed in 16 healthy male volunteers in a 2-way crossover trial. The results showed that anastrozole did not significantly affect the area under the curve, clearance, half-life and unbound concentrations of S- and R-warfarin. Additionally, anastrozole did not produce clinically relevant changes in the pharmacodynamic effects of warfarin.

The effect of anastrozole on antipyrine (a marker substrate of CYP activity) PK was assessed in 24 post-menopausal women (n = 12 each for anastrozole and placebo groups). No significant differences were noted in antipyrine PK parameters, compared to placebo.

The effect of cimetidine (non-specific inhibitor of various CYP enzymes) on anastrozole PK was assessed in 13 post-menopausal women. Cimetidine did not significantly affect anastrozole PK parameters.

These data show that anastrozole has no interaction with these commonly used drugs and marker substances; this is an important property for a drug potentially to be used in the long term adjuvant treatment of breast cancer.

[1] Grimm SW and Dyroff MC. *Drug Metab. Dispost.* 25, 598–602 (1997)

P101 Randomized trial of two versus four years of adjuvant tamoxifen (AT) for postmenopausal women with node positive breast cancer

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Randomized trials of AT for early stage breast cancer have shown significant reductions in the annual rates both of recurrence and of death. Most of these trials compared 1 or 2 years of AT with no adjuvant treatment. A controversy exists about the optimum duration of AT.

Patients and Methods: In 1986 we began a prospective randomized study to compare the efficacy of two different time-span of AT. Women were eligible for the study provided that they had 60–75 years old with primary breast cancer and positive axillary nodes which primary surgery was a modified radical mastectomy. Tamoxifen, 20 mg per day, was initiated within 60 days after mastectomy. No other type of adjuvant therapy was allowable. All patients without recurrence in the first two years were randomly assigned to continue or not AT for two further years.

Results: 288 women were randomized to one of the two schedules. Baseline characteristics were similar but in four years AT group there was a some larger proportion of women with 4 or more positive nodes (40% vs. 32%, $p = 0.158$). With a median follow-up of 5 years, 113 patients have recurred (62 of 142 undergoing AT for two years, and 51 of 146 undergoing AT for four years). Estimated five years – from randomization- disease free survival (DFS) was 55% for the 2 years AT group and 66% for the 4 years AT group ($p = 0.036$). When nodes group (1–3 vs. 4 or more) was accounted for in Cox's proportional hazards model, the effect of prolonged AT treatment on DFS remained significant (hazd ratio 2 vs. 4 years, 1.310, $p = 0.007$). When all causes of death were considered, the difference in overall survival among both groups of AT was not significant ($p = 0.329$). Multivariate analysis showed that 4 or more positive nodes ($p = 0.003$) and age ($p = 0.025$) were related with a significantly inferior overall survival.

Discussion: Our results suggest that, in relation to two years, four years of AT does improve the DFS in this group of women. The reduction of risk is similar to other study on this topic and the benefit is alike for both groups of nodes. We fail to detect significant differences in overall survival, competing causes of death and a still short follow-up could justify these results.

P102 Adjuvant high-dose medroxyprogesterone acetate (HD-MPA) for early breast cancer. 13 Years update of a multicenter randomized trial

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260 node negative (NN) and 281 node positive (NP) early breast cancer patients were randomized after adequate surgery to receive either no further medical treatment (group A) or an hormonotherapy with HD-MPA (500 mg IM daily for 4 weeks the 500 mg twice weekly for the next 5 months) (group B). NP patients received also 6 monthly courses of IV CMF. Patients characteristics were well balanced among both groups. Toxicity of MPA was manageable (weight increase in most patients and usual side-effects linked to progestin use in a maximum of 16% of patients in group B). In NN patients, at 13 years median follow up, relapse free survival (RFS) was significantly improved in HD-MPA arm (A: 0.54 vs B: 0.69 – p 0.004). This was observed for the whole group as well as in all prognostic sub-categories (age <50; > = 50; menopausal status; T; receptor categories; type of surgery). Differences were less striking in > = 50 years patients, as RFS curves tended to join. These differences in RFS were translated in a survival benefit in younger patients (A: 0.65; B: 0.81 – p 0.06). In the NP group, RFS and overall survival (OS) were not different at the whole group level or as regard T, number of positive nodes, receptor categories, type of surgery or radiotherapy. However a striking difference was observed when patients were split according to age (<50; > = 50) or menopausal status. If older patients benefited from the combined treatment (at 13 years RFS: A: 0.34, B: 0.59 – 0.002; OS: A: 0.48, B: 0.56), younger patients had a significantly worse prognosis when treated with CMF + HD-MPA, (at 13 years: RFS: A: 0.64, B: 0.34 – $p < 0.01$; *OS: A: 0.77, B: 0.54* – $p < 0.01$). These results were observed despite the fact that, irrespectively of age, MPA-treated patients could tolerate higher dose-intensities and dose-intensity procucts of CMF.

In conclusion, a clearcut adjuvant impact of HD-MPA was evidenced namely in <50 years NN early breast cancer, ie, in *premenopausal patients.* However, in less than 50 years NP patients, HD-MPA had a negative adjuvant impact both on RFS and OS. These results contrast with the results obtained in older NP subjects and with the significant adjuvant impact of HD-MPA observed in NN patients.

P103 What threshold for adjuvant tamoxifen in older breast cancer patients? A decision analysis

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Background: The consensus panel on the last St-Gallen conference tried to define adjuvant treatment according to risk categories. In the lowest risk category, the decision between no treatment or hormonotherapy was left optional. This study looks at the threshold risk of relapse (RR) at which tamoxifen offers benefit, and the threshold at which a 1% benefit in 5 or 10 years relapse rate or survival is obtained in older women. We studied also the way these threshold were influenced by the level of comorbidity.

Methods: A Markov model analysis was conducted. Data from the litterature retrieved by Medline and cross references were used. We hypothesized 5 years of tamoxifen use in receptor positive tumors.

Results: In women up to the age of 85, the threshold for an absolute positive effect on survival was minimal. The threshold RR allowing for a 1% reduction in mortality at 10 years was a 12% 10 years RR for a healthy 65 years old patient, and 21% for a patient in poor health. At 85 years, a 1% benefit in 10 year mortality cannot be obtained. However, for a 1% reduction in mortality at 5 years, the threshold 10 year RR is 31% for a healthy patient and 39% for a sick patient. Reduction in relapse is much less sensitive to age and comorbidity. For a 1% gain in relapse at 5 years, the threshold RR is 7% in a healthy 85 years old patient and 8% in a sick patient.

Conclusions: The threshold for a 1% improvement in 10 years relapse-free survival or overall survival is near the limit between minimal and low risk tumors in the St Gallen recommendations for healthy elderly with hormone-receptor positive breast cancer. For patient in their eighties, quality of life issues become a major consideration, since tamoxifen will decrease the rate of relapse without a major impact on survival in low-risk tumors.

P104 Adjuvant chemotherapy plus alternated hormonal therapy (AVCF-TM) for HR+ N+ breast cancer: 13-Year results of a randomized phase III trial

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Adjuvant AVCF (Doxorubicin 30 mg/m^2 IV d1, Vincristine 1 mg/m^2 IV d2, Cy-