Result: Fluorescence colorization were noticed on breast cancer cells. Besides it is easy to differentiate lymphocytes from cells of positive telomerase activity by way of morphology and color differences.

Conclusion: It is suggested that in situ TRAP method combined with cytologic diagnosis makes a great contribution to the improvement of diagnostic accuracy and the decrease of judged difference among persons and institutions.

Thursday, 1 October 1998 16:00-18:00

PARALLEL SESSION

Endocrinology

376 INVITED

Update on endocrine approaches in the treatment and prevention of breast cancer

M. Kaufmann. *Department of Gynecology and Obstetrics, Johann Wolfgang Goethe University Hospital of Frankfurt, Germany*

During the last 100 years endocrine procedures and agents became more and more important in the treatment and prevention of breast cancer.

The choice of endocrine drugs depends on the stage of disease, menopausal-status of the women, steroid hormone-receptors, and the toxicity profile of the drug.

In metastatic breast cancer patients endocrine therapy was the first effective palliative treatment and is also today's treatment of choice for low risk situation.

Along with adjuvant (post-operative) endocrine treatment with or without cytotoxic drugs it has been shown to improve disease-free and overall survival rates of primary breast cancer patients.

Neoadjuvant (primary or pre-operative) endocrine treatment is currently under investigation in the elderly patients to achieve more breast conserving surgery and better survival rates. Contrary to cytotoxic treatment endocrine therapy is active on tumor cells through distinct and highly selective mechanisms.

In the future endocrine treatment (e.g. tamoxifen, raloxifen, SERMS) will also play a major role for the prevention of breast cancer.

377 ORAL

Increased risk of recurrence for patients with EGFR and HER-p185 positive tumours when treated adjuvantly with tamoxifen for one year

A. Knoop[1], S. Bentzen[2], M. Nielsen[1], B. Rasmussen[3], C. Rose[1]. [1]*Dept. of Oncology, University Hospital, Odense;* [2]*Dept. of Experimental Clinical Oncology, University Hospital, Aarhus;* [3]*Dept. of Pathology Roskilde County Hospital, Denmark*

Aim: The aim of this study was to investigate interactions between treatment with tamoxifen and steroid receptor content and EGFR, HER-p185 and p53.

Methods: 1,716 high-risk postmenopausal breast cancer patients, who were all treated with irradiation, were randomly assigned to treatment with tamoxifen (868 women) or observation (848 women). The contents of the steroid receptors and expression of p53, EGFR, and HER-p185, were determined by immunohistochemistry. The follow-up time was 10 years. The endpoint was disease-free survival.

Results: Multivariate analysis demonstrated independent risk of disease for EGFR and HER-p185 positive high-risk patients and a decreased risk of disease in steroid receptor positive patients or patients with many positive lymph nodes when treated with tamoxifen. Patients with p53 positive tumours had an increased risk of disease, independent of adjuvant treatment with tamoxifen.

Conclusion: In patients with tumours positive for HER-p185 or EGFR another treatment than tamoxifen could be considered.

378 ORAL

Idoxifene antagonism of oestradiol-dependent MCF-7 breast cancer xenograft growth

S.R.D. Johnston[1], M. Dowsett[1], S. Riddler[2], M. Jarman[2]. [1]*Department of Academic Biochemistry, Royal Marsden Hospital;* [2]*Institute of Cancer Research, London, England*

Purpose: Idoxifene is a novel selective oestrogen receptor modulator (SERM). We have previously shown idoxifene to have significantly greater inhibition of ER+ve MCF-7 xenograft growth in comparison with tamoxifen (TAM) when given in the absence of oestradiol (E2), (Br J Cancer 1997 75; 804–809). In our current study we compared the antagonist effects of idoxifene with TAM in MCF-7 xenografts whose growth continued to be supported with E2. In addition, we compared the activities of the cis and trans forms of idoxifene. Cis-idoxifene has a 50-fold lower relative binding affinity (RBA 0.25) for ER than either trans-idoxifene (RBA 12.5) or TAM (RBA 5).

Methods: 95 tumours were established with E2 support in ovariectomised athymic mice and after 4 weeks were randomised to either continued E2, cis-idoxifene + E2, trans-idoxifene + E2, TAM + E2, or withdrawal of E2. Drugs were delivered in equimolar doses by implanted silastic capsule changed every 8 weeks.

Results: Tumour growth continued with E2 and regressed exponentially upon E2 withdrawal, confirming the hormone-dependence of this model. Cis-idoxifene had no effect on E2-dependent tumour growth. In contrast, both trans-idoxifene and TAM significantly inhibited E2 dependent growth ($p < 0.0001$), and tumour volumes remained static over the subsequent 12 weeks of the experiment. Uterine weights in animals treated with either transidoxifene + E2, or TAM + E2 were significantly ($p < 0.009$) less than those treated with E2 alone.

Conclusions: These data show that idoxifene and TAM are equivalent in their ability to antagonise E2-dependent MCF-7 xenograft growth and therefore support the potential clinical utility of idoxifene in the treatment of breast cancer. Furthermore, these studies suggest that idoxifene's antagonist activity on tumour growth correlates well with its binding affinity for ER.

(Supported by SmithKline Beecham Pharmaceuticals)

379 ORAL

Ocular toxicity from standard dose adjuvant tamoxifen therapy

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Purpose: Ocular toxicity due to Tamoxifen is a recognised side effect of the drug, but few studies have attempted to discover how common the problem is. The literature shows that most reports are in the form of individual case studies of symptomatic patients, whilst cross-sectional studies have used relatively small sample sizes, with a wide variability in incidence found (0–12%). This study was undertaken to determine the incidence of ocular toxicity in patients on standard dose adjuvant Tamoxifen therapy for breast cancer.

Methods: 840 patients have been examined for signs of characteristic keratopathy/retinopathy. Many aspects of visual function were assessed, including visual acuities and central visual fields.

Results: Ocular toxicity was found in 6.7% of patients: keratopathy in 3.7% and retinopathy in 3.0%. Visual function was affected in 22% of those cases. The cumulative dose required for ocular toxicity to occur varied from 3.6 to 75g, suggesting that the problem is not simply dose related.

Conclusion: It was found that signs of ocular toxicity can be seen in asymptomatic patients with good vision, suggesting the need for regular ocular examination in all patients on Tamoxifen. The evidence does not indicate the need to discontinue the drug, unless a reduction in visual function is found.

380 ORAL

Estrogen receptor α and β expression in human breast cancer tissues analysed by RT-PCR

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The details of correlation between estrogen receptor α (ERa) and β (ERb) expression in human breast cancers have not been clarified yet. We analyzed expression of both receptors by RT-PCR on 66 primary breast cancer

tissues from Japanese women. In a part of them, normal breast tissues were analyzed concomitantly. ERa was positive in 81.8% and 77.3% of primary cancers for exon 5 and 7, respectively, and ERb was positive in 54.5%. Among 49 positive for both exons of ERa, 26 were positive and 23 were negative for ERb. Among 8 negative for both exons, respective 4 were positive and negative for ER b. Thus no correlation was observed between expression of ERa and ERb in cancer tissues. While all 8 of normal breast tissues expressed ERa, ERb was positive in only 5 of them. The expression of ERb in normal tissues did not coincided with that in cancer tissues from same breast. The expression (i.e.; function) regulations of ERa and ERb in human breast tissues, therefore, seemed to be mediated by different mechanisms irrespective of their pathological characteristics.

381 ORAL

Urokinase-like plasminogenactivator (uPA) and plasminogenactivator-inhibitor type 1 (PAI-1) in primary breast cancer – Predictive markers for tamoxifen resistance?

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Estrogen and progesterone receptor status are established predictive factors for response to endocrine treatment in the adjuvant and palliative situation. Overexpression of the new prognostic factors uPA and PAI-1 have been reported to be predictive of resistance to Tamoxifen in metastatic disease.

We evaluated from our data the impact of uPA and PAI-1 on hormonal treatment. uPA and PAI-1 were determined out of fresh tumor specimens using a commercially available assay (Immunobind®-ELISA from American Diagnostica). 178 patients with primary breast cancer stage I, II or III received endocrine treatment with Tamoxifen 30 mg. Decision about treatment was not influenced by knowledge of uPA or PAI-1. Median follow-up was 27 months. Statistic analysis was done by Kaplan-Meier-estimates for survival data and Mann-Whitney-Test for cross-checks of distribution. Multivariate analysis was performed with the Cox-Regresion-Model.

Overexpression of uPA (>3.0 ng/mg protein) was present in 49%, overexpression of PAI-1 (>14.0 ng/mg protein) in 41% of all cases. Overexpression of uPA and PAI-1 was significantly correlated with higher nuclear grading ($p = 0.02$) and overexpression of PAI-1 with lower estrogen receptor expression ($p = 0.01$). Age, progesterone receptor expression, tumor stage, nodal stage were equally distributed between tumors with or without overexpression. Recurrence free survival (DFS) was 53 months for patients with uPA-overexpression versus 49 month in the control group ($p > 0.05$, n.s.), for patients with or without PAI-1 overexpression DFS was 51 months ($p > 0.05$, n.s.). Multivariate analysis for DFS and overall survival revealed only number of positive lymphnodes as predictive factor for recurrence or death

In this study endocrine treated patients in the adjuvant situation with overexpression of uPA or PAI-1 had no worse prognosis than patients without overexpression. uPA and PAI-1 overexpression were not predictive for Tamoxifen-resistance.

382 ORAL

Hormone replacement therapy does not influence pathological stage of breast cancer in 1113 tumours

S. Stallard[1,2], J. Litherland[1], C. Cordiner[1], E. Mallon[3], H. Dobson[1], W.D. George[2], D.J. Hole[4]. *[1]West of Scotland Breast Screening Centre; Depts of [2]Surgery; [3]Pathology, Western Infirmary; [4]West of Scotland Cancer Surveillance Unit; Glasgow, UK*

Women using Hormone Replacement Therapy (HRT) at diagnosis of breast cancer have been reported to have smaller more node negative tumours of better grade and to have lower mortality than non users. We have shown that significantly more women using HRT when they were screened developed interval cancers compared to non users. It is therefore important to include interval cancers in any study of the possible HRT effect on tumour type, size, grade and nodal status.

1113 women aged between 50 and 65 years were screened between 1988 and 1993 and either had a screen detected cancer (SDC) (816 women) or developed an interval cancer (297 women) up to the end of 1996. Current HRT usage was recorded at the time of screening and also at presentation with breast cancer. Of the 816 women with SDC 100 (12.3%) were using HRT when they were screened. Of the 297 women who developed interval cancers 66 (22.2%) were currently taking HRT at diagnosis. Of the 1113 women studied therefore 166 women (15%) were HRT users when they developed breast cancer. There were no significant differences in the type, size or grade of tumours or nodal status comparing HRT users with non users. These results do not support the commonly held belief that HRT users develop tumours with favourable prognostic features.

383 POSTER

Women taking hormone replacement therapy develop low grade tumours

J. Iddon, C. Harding, C. Boggis[1], N.J. Bundred. *Department of Surgery; [1]Department of Radiology, UHSM, Manchester, UK*

Women taking hormone replacement therapy (HRT) are said to have a higher risk of developing breast cancer but the tumours they develop may be of a lower grade. In order to remove any bias introduced by pre-existing subclinical tumours, the impact of HRT on the development of breast cancer was assessed by studying women who had cancers detected at routine screening mammography subsequent to normal mammograms.

372 women had such tumours detected between 1.1.91 and 1.7.97. Patients who went on to have treatment outside the region (59) were excluded from the study.

Data regarding brand of HRT, dose and duration of use was collected along with details of tumour pathology such as size, grade, lymph node status and presence of carcinoma in situ (CIS). Women who had previously taken HRT but had stopped were excluded, then women who were taking HRT at the time of diagnosis (80) were compared with those who had never taken HRT (202).

Overall, women on HRT were found to have lower grade tumours than those not taking HRT, $p = 0.05$ X2 test, and women with lower grade tumours had been taking HRT for longer, grade 1 = 72 months ± 74.3, grade 2 = 53 ± 36.7, grade 3 = 40 months ± 32.8. There was no relationship between HRT use and tumour size (users 13.59 mm ± 8.22, non-users 15.95 mm ± 9.95), lymph node positivity, or CIS, although there was a trend in women taking HRT to have CIS around the tumour.

In conclusion, tumours which develop in women taking HRT are more likely to be of a lower grade and may be associated with carcinoma in situ.

384 POSTER

Change in expression of ER and BCL-2 predict for quality and duration of response in endocrine sensitive breast cancer

F.S. Kenny[1], P.C. Willsher[1], J.M.W. Gee[2], R.I. Nicholson[2], I.O. Ellis[1], J.F.R. Robertson[1]. *[1]City Hospital Nottingham; [2]Tenovus Cancer Research Laboratories Cardiff, UK*

Aims: Pre-treatment oestrogen receptor (ER) status in human breast cancer is correlated with sensitivity to first-line endocrine therapy but is not accurate enough to predict for quality or duration of response. We have previously shown that ER expression is down-regulated during anti-oestrogen treatment. This study has investigated whether the degree of change in expression of ER and related biological markers determines for quality and duration of endocrine response.

Methods: 125 patients (61 Stage I–II elderly, 54 Stage III, 10 Stage IV) underwent sequential tumour biopsies at diagnosis, 6 weeks and 6 months for immunocytochemical assessment of ER, PgR, pS2 and bcl-2 expression whilst on primary tamoxifen. Response at 6 months was assessed by UICC criteria. 22 patients showed de novo resistance, 53 achieved static disease (SD), 43 partial response (PR) and 7 complete response (CR). Median follow-up is 46 months.

Results: Objective responders (OR) had significantly longer duration of response (DofR) than SDs ($p = .0016$). Greater % fall in ER H-score between pre-treatment level and both 6 weeks ($p = .035$) and 6 months ($p = .046$) was significantly associated with better quality of response (OR vs SD). Greater % reduction in bcl-2 H-score ($p = .038$) and ER H-score ($p = .029$) at 6 weeks were significantly correlated with longer DofR. The sub-set of ORs displaying greatest fall in ER H-score at 6 weeks ($n = 17$) achieved longest DofR of all responders ($p = .008$).

Conclusion: We believe this to be the first study to demonstrate that degree of change in expression of ER and the related biological marker bcl-2 predict for quality and duration of response in endocrine sensitive breast cancer.