tention (ADOC) but no cardiac events were observed. Therapy was stopped preterm in 36 P (ADOC 17, AC-DOC 19) because of toxicity (17 pts), progression (4 pts), death (1 pts), other causes (5 pts), and for lack of compliance (9 pts). Overall breast conservation rate was 75.8%. In 56 of 378 pts. (14.8%) a pCR with no detectable viable and/or in situ tumor cells was achieved. Interim analysis on 378 pts. has revealed an extensive difference in pCR -rate between both study arms. The recruitment was stopped according to the DMC recommendation.

Conclusion: Dose dense and sequential adriamycin/docetaxel regimens have acceptable toxicities but show a considerable difference in efficacy.

211 POSTER

Weight change in premenopausal breast cancer (BC) women at ≥12 months after diagnosis

J. Wojtacki[1], G. Rolka-Stempniewicz[1], K. Leśniewski-Kmak[2], K. Czyżewska[1], D. Filarska[1], M. Śliwińska[1], M. Wróblewska[1], A. Hyży-Topolewska[1], M. Góralczyk[1]. [1] *PCK Maritime Hospital, Gdynia;* [2] *Military School of Medicine, Warsaw, Poland*

Introduction: Weight change in patients with BC is widely observed, but poorly described clinical problem. The study is aimed at estimating the frequency and risk factors for weight change at least 1 year after primary diagnosis of BC.

Material and Methods: Weight was measured in 189 premenopausal BC women (median age: 37 yrs, range: 32–53) at diagnosis and ≥12 months afterwards (range: 12–19, median: 14.5). All patients were primary mastectomized and 72% of them (N = 136) have received adjuvant therapy (chemotherapy - 93, chemotherapy and tamoxifen 43, locoregional radiotherapy - 87), while 28% (N = 53) were assigned to observation. All study participants were clinically free of disease during analysis period.

Results: The median weight change in the study group was +2.7 kg (range: −3.0–+17.2 kg). Treated women gained significantly more weight than patients in observed population (7.1 vs. 1.9 kg, respectively; $p < 0.001$). Weight gain of at least 1.0 kg was noticed in 67% (N = 127) patients and was significantly more frequent in treated women as compared to the observation group (74% vs. 47%; $p < 0.01$). In patients who received adjuvant therapy, the prevalence and magnitude of weight gain were not associated with estrogen receptor status, primary tumor size, axillary lymph nodes status, inclusion of radiotherapy or duration of tamoxifen administration. Weight gain of ≥1 kg occurred more frequently in initially obese women as compared to those with normal weight ($p < 0.002$), patients treated with tamoxifen ($p < 0.05$) and CMF regimen as compared to anthracycline-containing chemotherapy ($p < 0.01$) as well as in those who developed amenorrhea ($p < 0.003$).

Conclusion: Our data confirmed that weight gain is observed in the great majority of BC women receiving adjuvant therapy and suggest that risk factors for it may include treatment with tamoxifen and CMF regimen, initial obesity and induction of amenorrhea with chemotherapy.

212 POSTER

Acute and late toxicity following adjuvant high-dose chemotherapy for high-risk primary operable breast cancer

I.M. Svane[1], K.M. Homburg[2], C. Kamby[1], D.L. Nielsen[1], O. Roer[1], D. Sliffsgaard[1], H.E. Johnsen[3], S.W. Hansen[1]. [1] *Herlev Hospital/Copenhagen University, Department of Oncology, Herlev, Denmark;* [2] *Odense University Hospital, Department of Clinical Immunology, Odense, Denmark;* [3] *Herlev Hospital/Copenhagen University, Department of Haematology, Herlev, Denmark*

Background: Patients with node-positive breast cancer are at greater risk for relapse compared to node-negative patients. To improve outcome, high-dose chemotherapy with haematopoietic stem cell support was employed from 1996 to 2000 at Herlev Hospital as an adjuvant treatment strategy for management of primary high-risk breast cancer patients with more than five positive nodes. As available data indicate at most a marginal benefit of high-dose therapy we find it relevant more thoroughly to document the morbidity, as well as the requirement of supportive therapy associated with high-dose treatment.

Study: This single institution study included 52 women aged * 56 years with primary operable breast cancer and more than 6 tumour-positive axillary lymph nodes. The treatment regimen consisted of at least three initial courses of FEC (5-Fluorouracil 500 mg/m2, Epirubicin 90 mg/m2, Cyclophosphamide 500 mg/m2) followed by high-dose chemotherapy (Cyclophosphamide, Thiotepa, Carboplatin, STAMP-V) supported by autologous peripheral blood stem cell reinfusion. Furthermore, patients received radiotherapy (2 Gy x 24). Data regarding organ toxicity were processed for evaluation of short and long-term side effects associated with the treatment regimen.

Results: No treatment related death occurred. There was substantial acute toxicity including frequent catheter-related infections. Long-term toxicities included reduced lung diffusion capacity (n=36), fatigue(n=14), arthralgia/myalgia (n=10), neurotoxicity (n=9) and memory loss (n=4). However, most toxicities were grade 1-2 and reversible within two years. The majority of patients regained working ability after one year. Quality assessment of the stem cell graft revealed cytokeratin 19 positive tumor cells in 3 of 37 tested patients (8%). Within a median follow-up of 30 months (range, 11-57), 25% of the patients had relapsed. Recurrence free survival was 75% and overall survival was 88% three years after treatment start.

Conclusion: Our main objectives were to assess toxicity and the applicability of the HDC strategy. Apart from two isolated cases of severe renal and pulmonary toxicity the high-dose treatment was relatively well-tolerated without serious organ toxicity and without toxic deaths. Thus, the treatment was found to be feasible with manageable toxicity and an acceptable requirement of supportive therapy.

Thursday, 21 March 2002 16:30–18:00

PROFFERED PAPERS

Targeted therapies

213 ORAL

Safety of Herceptin monotherapy administered on a 3-weekly schedule: preliminary data from a phase II study in women with HER2-positive metastatic breast cancer

J. Baselga[1], N.-J. Castañeda-Soto[2], M. Clemens[3], M. Green[4], V. Harvey[5], C. Barton[6], S. Morales[7]. [1] *Hospital Vall d'Hebron, Department of Medical Oncology, Barcelona, Spain;* [2] *Instituto Nacional de Cancerologia, Clinica de Mama, Tialpan, Mexico;* [3] *Mutterhaus der Borromaeerinnen, Haematologie/Onkologie, Trier, Germany;* [4] *Royal Melbourne Hospital, Department of Medical Oncology, Melbourne, Australia;* [5] *Auckland Hospital, Oncology Department, Auckland, New Zealand;* [6] *Roche Products Ltd, Welwyn Garden City, UK;* [7] *Oncology, Hospital Arnau de Vilanova, Lleida, Spain*

Background: The standard weekly dosing regimen of Herceptin, alone or with paclitaxel, is well tolerated and efficacious. However, less frequent dosing would be more convenient and also logical, in view of the long terminal half-life of Herceptin (28.5 days). A 3-weekly schedule of Herceptin has been shown to be well tolerated in combination with 3-weekly paclitaxel. This study examines the same 3-weekly schedule of Herceptin given as monotherapy.

Methods: Women with previously untreated HER2-positive (IHC 3+ or FISH positive) metastatic breast cancer and left ventricular ejection function (LVEF) >50% were eligible. All patients were treated with Herceptin 8mg/kg i.v. loading dose, followed by 6mg/kg every 3 weeks. The primary objective is response rate, with time to progression, rate of symptomatic heart failure and serious infusion reactions, and pharmacokinetics (PK) as secondary objectives.

Results: At the time of reporting, 91 patients had entered the study. One patient did not receive Herceptin and is excluded. Mean patient age was 53 (23-84) years; 43% of patients had lung and 38% had liver metastases; 71% had received prior adjuvant chemotherapy; 46% had received anthracyclines. 71 patients were known to have centrally confirmed HER2-positive disease (IHC 3+, FISH positive or both). Patients had received a median of 4 (1-13) cycles of 3-weekly Herceptin and 45 patients had discontinued therapy (42 due to progressive disease/insufficient therapeutic response, 2 due to death and 1 due to an adverse event). Therapy has been well tolerated, with most side effects mild to moderate in severity. No unexpected adverse events were encountered. Only 17 NCI-CTC grade 3 and two grade 4 events (cerebrovascular accident and cardiac tamponade, both unrelated to Herceptin) have occurred. Baseline LVEF was 63% (49-84%) and no patient has developed symptomatic cardiac failure. Preliminary data have shown that patients with very high ECD concentrations at baseline have correspondingly low serum concentrations of Herceptin. Further PK and preliminary efficacy data will be presented.

Conclusions: Administration of Herceptin every 3 weeks, at 3 times the standard dose, is a well-tolerated alternative dosing regimen that merits further investigation.

214 ORAL

Cardiotoxicity associated with Herceptin (trastuzumab) therapy: A potential mechanism

C. Zuppinger[1], D.B. Sawyer[2], T. Miller[2], H.M. Eppenberger[3], T.M. Suter[1].
[1] *University Hospital Bern, Cardiology, Bern, Switzerland;* [2] *Boston University Department of Medicine, Myocardial Biology Unit, Boston;* [3] *Federal Institute of Technology (ETH), Institute of Cell Biology, Zurich, Switzerland*

HER2 is a transmembrane tyrosine kinase growth factor receptor that is overexpressed in approximately 20% of breast cancers. HER2 overexpression/amplification is associated with poor prognosis, including reduced relapse-free and overall survival. Herceptin (Trastuzumab) is a humanized monoclonal antibody that specifically targets HER2-positive breast cancer cells. Overall, safety data collected from pivotal trials with Herceptin indicate that this therapy is generally well tolerated and associated with a low incidence of chemotherapy-related side effects. However trials with the combination of Herceptin plus chemotherapy, in particular anthracyclines, have revealed an increase in the occurrence of cardiac toxicity. Retrospective analysis of the data suggests that the cardiotoxicity observed may represent exacerbation of stress-induced cardiotoxicity, and that in the majority of cases the cardiotoxicity is both generally reversible and manageable with standard medical treatment. The pathophysiology of cardiotoxicity associated with Herceptin therapy remains unclear. We therefore used an in vitro system of adult rat ventricular cardiomyocytes (ARVM) to examine the potential mechanisms for the reported cardiotoxicity of Herceptin in patients with concurrent anthracycline treatment.

Doxorubicin (0.1 to 0.5 uM) induced in ARVM in culture a 10-fold increase in myofibrillar disarray as assessed by immunostaining for myomesin and filamentous actin ($p<0.0001$ vs. control, n=8). Both neuregulin-1beta (NRG-1beta, an agonist of HER2) and anti-HER2 (clone B10, a rat-specific analogue to trastuzumab) caused rapid (10 minutes) activation of HER2 and Erk1/2 in ARVM, while NRG-1beta but not anti-HER2 activated Akt kinase. Concomitant treatment of myocytes with anti-HER2 and doxorubicin caused a 60% increase in myofibrillar degeneration and disarray vs. doxorubicin alone (n=8, $p<0.05$). In contrast, activation of HER2 by NRG-1beta decreased anthracycline-induced disarray by 33% (vs. doxorubicin alone, n=8, $p<0.05$).

Therefore, the reciprocal regulation of anthracycline-induced myofilament disarray by anti-HER2 and NRG-1beta suggests that the NRG-1beta/HER2 signaling in the heart is an important determinant of myofibrillar response to stress, and offers a potential mechanism for the observed cardiotoxicity of Herceptin. Moreover, this data suggests potential therapeutic strategies for the prevention of anthracycline and trastuzumab induced heart failure.

215 ORAL

Fulvestrant (Faslodex®) is effective in postmenopausal women with visceral metastases (VM) in advanced breast cancer (ABC)

L. Mauriac. *Bergonie Institute, France*

Fulvestrant (Faslodex®, FAS) is a novel Estrogen Receptor Downregulator. Two Phase III trials have examined the efficacy and safety of a once-monthly intramuscular injection of FAS 250 mg vs a once-daily 1 mg oral dose of anastrozole (Arimidex®, AN) in postmenopausal women with ABC progressing on prior endocrine therapy. A combination of results from both trials was prospectively protocolled to allow the effectiveness of FAS and AN to be assessed in those patients with VM. The number of VM lesions was equally distributed between the trials and FAS and AN. Efficacy was classified as an objective response (OR) - defined as a complete response (CR) or partial response (PR) - or as gaining clinical benefit (CB) - defined as CR, PR or stable disease $\geq$24 weeks. VM were present in 381 patients (44.7%); FAS and AN were equally effective in all patients with VM (OR: 15.7% vs 13.2% and CB: 38.2% vs 37.4%, respectively), in patients with only VM (OR: 18.8% vs 14.0% and CB: 49.2% vs 41.9%) and in patients without VM (OR: 21.9% vs 19.3% and CB: 47.6% vs 43.8%). Median DOR reflected these findings. No statistical analysis was performed on the DOR results.

	Median duration of response (months)	
	FAS 250 mg	AN 1 mg
OR, all patients with VM	17.5	11.7
with only VM	17.5	11.7
without VM	14.3	13.7
CB, all patients with VM	11.0	8.9
with only VM	10.8	9.1
without VM	14.3	13.7

These data show that FAS is effective in ABC patients failing on prior hormonal treatment and the therapeutic effect is also particularly evident in patients with VM.

216 ORAL

Postmenopausal women with advanced breast cancer who have progressed after fulvestrant (Faslodex®) remain sensitive to other endocrine agents

I. Vergote. *University Hospital, Leuven, Belgium*

Fulvestrant (Faslodex®, FAS) is the first in a new class of endocrine agents, an Estrogen Receptor (ER) Downregulator, which dramatically reduces cellular levels of the ER. Two Phase III trials have shown FAS to be at least as effective as anastrozole in the treatment of advanced breast cancer in postmenopausal women progressing on prior endocrine therapy. A total of 423 patients from both trials, who had progressed on endocrine therapy, usually tamoxifen, received FAS 250 mg as a once-monthly intramuscular injection. We present retrospective follow-up data from patients who had clinical benefit on FAS (complete response, CR; partial response, PR; stable disease $\geq$24 weeks, SD) and after disease progression, received alternative endocrine therapy.

	Number of patients			
	Total	PR	bfseries SD	bfseries Progression
Endocrine therapy	57	4	23	30
Aromatase inhibitors	49	3	18	28
Megestrol acetate	8	1	5	2

Fifty-seven patients progressed on FAS and received subsequent endocrine therapy. The majority of patients received an aromatase inhibitor (n = 49: anastrozole n = 40; letrozole n = 9), which resulted in a PR in three patients, SD $\geq$ 24 weeks in 18 patients and progression in 28 patients. In conclusion, these data demonstrate that after progression on FAS, patients remain sensitive to other forms of endocrine therapy. FAS provides an additional treatment option that may extend the time window of endocrine therapy before cytotoxic chemotherapy needs to be considered.

217 ORAL

A novel antiestrogen, TAS-108 (SR16234) shows full antagonistic activity to ER alpha and beta with a unique mechanism

Y. Yamamoto[1,2], O. Wada[1], J. Yanagisawa[1], S. Kato[1], K. Kitazato[2].
[1] *Institute of Molecular and Cellular Biosciences, University of Tokyo, Tokyo, Japan;* [2] *Cancer Research Lab., Taiho Pharmaceutical Co., Ltd.*

TAS-108 is a novel steroidal antiestrogen entering the stage of clinical evaluation in the area of breast cancer based on its promising growth inhibition of breast tumors, including tamoxifen resistant tumors, and protective effects to bone skeleton and cardiovascular systems in animal models. To explain its multiple biological effects, the molecular mechanism(s) of action of TAS-108 mediated through the ER alpha and/or beta were analyzed and compared with the other antiestrogens. TAS-108 strongly suppressed the transcriptional activation of the estradiol (E2)-liganded estrogen receptor (ER) alpha and beta, showing the potency similar to that of pure antiestrogen, faslodex. Both TAS-108 and faslodex liganded ERs have no transcriptional activity, contrasting the properties of 4-OH tamoxifen and raloxifene, which showed the transcriptional activity, considered being the AF-1 activity. The ligand-dependent transcriptional activity was also examined using mutanted ER alpha, designed as D351Y and derived from tamoxifen resistant cell line. TAS-108 and faslodex inhibited the transcriptional activity mediated by the D351Y, contrasting the effects of E2, 4-OH tamoxifen and raloxifene, which promoted the transcriptonal activities. Therefore, TAS-108 and faslodex show an ability to overcome tamoxifen resistance caused by D351Y mutation. However, the full antagonistic activity of faslodex is caused by prevention of binding of the liganded-ER alpha to DNA while the TAS-108 lacks such ability, as shown by the gel shift assay method. Despite the presence of a common steroidal structure, the protease digestion method revealed that the digestion patterns of the TAS-108 liganded ERs are different from those of E2 and faslodex, but similar to that of 4-OH tamoxifen. Since the co-activators or co-repressors modify transcriptional activity of the ERs, a mammalian two-hybrid assay was employed and revealed that

TAS-108 recruited a co-repressor, SMRT, to ERs more strongly than 4-OH tamoxifen and raloxifene. Based on these findings, we concluded that TAS-108 could be classified as a unique antiestrogen exerting the full antagonistic activity, even against tamoxifen resistant tumors, via co-repressor recruitment to ERs and its tissue selective activity is modulated the co-factors. These unique properties of TAS-108 are also shared by its active metabolite already found in animals and humans.

218 ORAL

The pharmacokinetics of darbepoetin and changes in endogenous erythropoietin in patients (PTS) with nonmyeloid malignancies receiving or not receiving chemotherapy

A. Heatherington, J. Schuller, D. Kotasek, J. Glaspy, R. Smith, R. Rovetti, G. Rossi. *AMGEN, Pharmacology-Pharmacokinetics Drug Metabolism, Thousand Oaks, CA, 91320, USA*

No data on their pharmacokinetic (PK) profile of recombinant human erythropoietin (rHuEPO) in cancer pts receiving chemotherapy is published; however, an increase in endogenous erythropoietin (eEPO) immediately after chemotherapy has been described. Darbepoetin alfa (Aranesp™) has an approximately 3-fold greater half-life relative to rHuEPO, and an associated increase in in-vivo biologic activity. The PK properties of darbepoetin alfa and the relationship with chemotherapy have been studied in 4 clinical studies. The studies enrolled pts (n = 810) with nonmyeloid malignancies either receiving (3 studies) or not receiving (1 study) chemotherapy.

The findings include:

(1) Darbepoetin alfa does not accumulate after multiple dosing once every 1, 2, or 3 wks.

(2) The PK of darbepoetin alfa are dose-linear and time-invariant across a wide range of doses.

(3) The effects of chemotherapy on the serum concentration of eEPO demonstrate that concentrations of eEPO rise in the 48 hr after the first administration of chemotherapy by greater than 126%.

(4) An increase associated with chemotherapy was also observed for darbepoetin alfa serum concentrations.

(5) When the kinetics of darbepoetin alfa were compared in cancer pts receiving or not receiving chemotherapy the mean concentration of darbepoetin alfa 48 hr after dose were consistently higher in pts receiving chemotherapy compared with those from pts not receiving chemotherapy.

The finding that cytotoxic chemotherapy may have an impact on the distribution, metabolism, or elimination of darbepoetin alfa or eEPO, may be of importance in the optimization of dosing/schedule efficiency for this agent.

219 POSTER

A phase III trial to determine the activity and safety of fulvestrant (Faslodex®) in premenopausal women with oestrogen-receptor positive breast cancer

J.F.R. Robertson[1], C. Lanza[2]. [1] *Nottingham City Hospital, Professorial Unit of Surgery, Nottingham, United Kingdom;* [2] *AstraZeneca, AstraZeneca, Alderley Park*

Fulvestrant (Faslodex®), the first in a new class of endocrine agents, the Estrogen Receptor (ER) Downregulators, has been demonstrated to significantly reduce cellular levels of ERs. Phase II trials have associated fulvestrant activity with a significant decrease in indices of tumour ER, progesterone receptor (PGR) and cell proliferation (Ki67 labelling), and two Phase III trials have shown fulvestrant to be effective in the treatment of advanced breast cancer in postmenopausal patients who have progressed following prior hormonal therapy. This new double-blind, placebo-controlled trial represents a 'proof of concept' study that will examine whether a single dose of fulvestrant also has antitumour activity in premenopausal breast cancer. Up to 80 premenopausal women with ER-positive primary breast cancer, who are undergoing curative-intent tumour resection surgery, will undergo a pre-treatment tumour biopsy during the eligibility screen to confirm ER status. Thereafter, the patients will be randomised to receive either fulvestrant 250 mg, administered as a single intramuscular injection, or placebo. Surgery will be performed 15-22 days later. The primary trial objectives will be to perform an immunohistochemical analysis of the tumour biopsies taken at screening and surgery to determine the three surrogate markers of clinical efficacy (ER, PGR and Ki67), and thereby the impact of fulvestrant treatment. Secondary objectives will include safety and tolerability assessments, and the measurement of pre- and post-treatment levels of circulating tumour cells and endocrinological variables such as luteinising hormone, follicle-stimulating hormone and progesterone. Significance will be assessed using analysis of covariance. To date 71 patients have been recruited. The trial is expected to report mid 2002. Fulvestrant is well tolerated in postmenopausal women; preliminary tolerability data in premenopausal women will be presented.

220 POSTER

A phase II study capecitabine (xeloda) in antracyclin-refractory, and antracyclin and docetaxel-refractory metastatic breast cancer (MBC)

T. Semiglazova, M.L. Gershanovich, V.V. Semiglazov. *Petrov Research Institute of Oncology, chemotherapy, St.-Petersburg, Russia*

Purpose: Capecitabine is novel, oral, selectively tumor-activated fluoropyrimidine carbamate. A phase II trial compared the efficacy, safety and tolerability of twice-daily oral capecitabine at 2,510 mg/m2/d given for 2 weeks followed by a 1 week rest period and repeated in 3-week cycles, in two group patients: A- antracyclin-refractory and B- antracyclin and docetaxel-refractory metastatic breast cancer.

Patients and Methods: Eighty patients were entered in trial. Both group of patients were to have received at least 2, but not more than 3, prior chemotherapeutic regimens for MBC (A -antracycline, n=49; B -antracycline and docetaxel, n=31).

Results: The overall response rate in the group A was 24.5%, including three complete responses (6.1%). The response rate observed in the group B was 20.7%, with no complete responses. Median time to progression was 6.5 months in the group A and 6.2 months in the group B. Survival was similar in the two treatment groups (10.0 and 8.1 months respectively). The most common treatment-related adverse events were hand-foot syndrome, diarrhea, nausea, vomiting and fatigue. The rates of adverse events were the same in both groups. Hand-foot syndrome and diarrhea occurred with grade 3 and 4 intensity were in 12% of patients in the group A and 10% - in the group B.

Conclusion: Capecitabine (Xeloda) is effective and well tolerated either in the treatment of antracyclin-refractory, and antracyclin and docetaxel-refractory metastatic breast cancer, and is suitable for outpatient therapy.

221 POSTER

Effects of anastrozole on lipid metabolism compared with tamoxifen – in vivo study

H. Sasanuma[1], Y. Hozumi[1], Y. Hakamata[2], S. Ogura[1], H. Nagai[1]. [1] *Jichi Medical School, General Surgery, Tochigi, Japan;* [2] *Jichi Medical School, Experimental Medicine, Tochigi, Japan*

Tamoxifen, a standard endocrine therapy agent, has been used for breast cancer patients. Its adverse effects, specially on lipid metabolism, are well known. Although the mechanism still remains mostly unknown, we previously reported that tamoxifen decreases the activity of lipoprotein lipase (LPL), a key enzyme of triglyceride metabolism, in clinical and experimental studies (J Clin Endocrinol Metab 1998, Horm Res 2000). Recently anastrozole, a new generation aromatase inhibitor, has been used for postmenopausal metastatic breast cancer. Several clinical trials of adjuvant treatment using this agent have started. However, the effect of anastrozole on lipid metabolism is unknown. The aim of this study is to evaluate the effect of anastrozole on lipid metabolism, especially LPL activity, compared with tamoxifen in an animal study.

Methods: Ovariectomized female rats were divided into six groups. 1; C (control) group. 2; T (tamoxifen treatment) group. 3; A (anastrozole treatment) group. 4; CAT (combination treatment of anastrozole and tamoxifen) group. 5; NAT (no treatment after tamoxifen) group. 6; AAT (anastrozole treatment after tamoxifen) group. Agent was orally administered for three weeks in all groups except for AAT group. In AAT group, rats were treated by tamoxifen for three weeks and subsequently by anastrozole for the following three weeks. Body weight was measured every day. Serum total cholesterol and triglyceride, and LPL activity of post heparin plasma were measured at the end of experiment. Adipose tissue weight of sacrificed animals was also measured.

Results: Body weight gain was reduced significantly only in T and CAT groups. In AAT and NAT groups, body weight increased after tamoxifen administration. Serum cholesterol levels were significantly lower in T and CAT groups than in C group ($P < 0.001$). Serum triglyceride levels were significantly higher in T group than in other groups ($P < 0.001$). LPL activity was significantly lower in T and AAT groups ($P < 0.05$). On the other hand, there was no significant difference in all these parameters in A group.

Conclusion: We conclude that anastrozole has no effects on lipid metabolism including LPL activity. There was little influence on lipid profiles

even using combination and subsequent treatment with tamoxifen. In a clinical setting, therefore, anastrozole might be administered safely to patients who show abnormal triglyceride profiles during tamoxifen treatment.

222 POSTER

The anticancer activity of a new antiestrogenic agent, TAS-108 (SR16234), against DMBA-induced mammary tumors in rats is partly mediated by deEt-TAS-108, its potent metabolite exerting a strong antagonistic properties

J. Shibata, T. Shindo, A. Hashimoto, K. Wierzba, Y. Yamamoto, K. Sakai, T. Toko, S. Yano, K. Matsuo, K. Kitazato. *Cancer Research Lab, Taiho Pharmaceutical Co., Ltd.*

TAS-108 showed the anticancer activity against human breast tumors and its tamoxifen resistant variant xenografts. TAS-108 exhibited a different conformation of the complex with estrogen receptors compared with other antiestrogens, like faslodex. Recent pharmacological studies have been performed in rats with DMBA-induced breast cancers to determine the range of its effective doses and accompanying plasma concentrations. The additional study involved the evaluation of anticancer activity of deEt-TAS-108, the metabolite persisting at high levels in the tumors.

Methods: The antitumor effects of TAS-108 were examined in rats with DMBA-induced mammary carcinomas, with simultaneous determination of its concentration in plasma, using a LC/MS/MS method. The antagonistic/agonistic activities of TAS-108 and deEt-TAS-108 were determined by measuring uterus weights of immature rats following 3-day treatment. The antitumor activity of deEt-TAS-108 was examined using MCF-7 human breast tumor xenografts.

Results: Oral daily treatment of tumor bearing rats with TAS-108 at the doses of 0.3 to 30 mg/kg for 28 days resulted in significant and dose-dependent tumor growth inhibition as demonstrated by T/C values of 0.40, 0.32 and 0.29 at doses of 3, 10 and 30 mg/kg, respectively. The plasma concentrations at these doses ranged from 13.9 to 61.6 ng/mL. Neither TAS-108 nor deEt-TAS-108 caused an increase of uterine mass of immature rats, contrasting the agonistic properties of tamoxifen observed at its effective dose range. Both compounds showed the same and high binding affinity to ERs. deEt-TAS-108 significantly inhibited the growth of MCF-7 human breast cancer in nude mice.

Conclusion: TAS-108 exhibits antitumor activity against the DMBA induced mammary carcinoma rat model at dose range as low as 3 mg/kg. The metabolite, deEt-TAS-108, strongly accumulating in the tumor tissue and possessing no agonistic properties, appeared to exert a potent anticancer effect, which contributes significantly to overall anticancer activity of TAS-108. Presumably, TAS-108 is a novel antiestrogenic agent for breast cancer patients lacking a low if any risk of inducing the uterine endometrial carcinoma.

223 POSTER

Fulvestrant (Faslodex™) as hormonal treatment in postmenopausal patients with advanced breast cancer (ABC) progressing after treatment with tamoxifen and non-steroidal aromatase inhibitors: An ongoing phase II SAKK trial

L. Perey, B. Thürlimann, H. Hawle, O. Bonnefoi, S. Aebi, D. Dietrich, A. Goldhirsch. *For the Swiss Group for Clinical Cancer Research (SAKK); CHUV, Lausanne, Switzerland*

Fulvestrant (Faslodex™; formerly ICI 182,780) is a new class of antiestrogen completely free of agonist activity. In postmenopausal women with ABC progressing on prior endocrine therapy, it has shown activity similar to anastrozole (A. Howell. Eur J Cancer 2001; 37 (Suppl 6): 151; Abstract 550). The present still ongoing multicenter trial conducted by the SAKK, aims at assessing the efficacy of fulvestrant 250 mg monthly as third-line treatment in ABC patients progressing after tamoxifen and non-steroidal aromatase inhibitors. After enrollment of 21 patients, inclusion criteria were modified to also include patients progressing after steroidal aromatase inhibitors. We report on the first 18 patients followed for at least 3 months. Median age was 67 years (range 45–85). The majority of patients had bone metastases (13 patients), 9 patients had liver metastases, skin and lymph node metastases were each seen in 3 patients and 2 patients had lung metastases. Eight patients received adjuvant chemotherapy and 5 patients had one line of chemotherapy for metastatic disease. All patients received anastrozole or letrozole as second-line treatment for ABC except 1 patient who received an aromatase inhibitor as first-line treatment after progression on adjuvant tamoxifen. Fulvestrant was well tolerated; side effects were mild (grade 1 and 2) and consisted of fatigue in 3 patients, chills in 3 patients, nausea and vomiting in 3 patients, constipation in 2 patients, hot flushes in 2 patients and stomatitis in 2 patients. In 2 patients, follow-up is too early for response evaluation. Ten patients presented with stable disease for at least 3 cycles. No objective response could be observed so far and 6 patients showed a progressive disease. Further update of response rate and tolerability will be presented.

224 POSTER

Pharmacokinetic studies on TAS-108 (SR 16234): Formation of a potent metabolite that specifically accumulates in the tumor

H. Yamaya[1], K. Yoshida[1], M. Saeki[1], K. Wierzba[2], J. Shibata[2], S. Yano[2], Y. Sato[3], A. Takao[3], K. Kitazato[2], K. Yamashita[1]. *[1] Taiho pharmaceutical Co., Ltd., Pharmacokinetics Research Lab.; [2] Taiho pharmaceutical Co., Ltd., Cancer Research Lab.; [3] Daiichi PureChemicals Co., Ltd., Research Center*

TAS-108 is a novel steroidal anti-estrogen, modulating the differential recruitment of transcriptional co-factors by the liganded-ERs, which represents a promising agent for the treatment of breast cancer. To confirm whether TAS-108 should enter clinical evaluation and further development, the studies on the plasma TAS-108 concentrations associated with optimal anticancer effects, the biotransformation profile, and the tissue distribution of the TAS-108 with particular attention to specific accumulation in the tumor and the other tissues controlled by the ERs.

Methods: After oral administration of 14C-labeled TAS-108 to the rats bearing DMBA-induced mammary tumors, plasma and tissue concentrations of TAS-108 and its main metabolites were determined by HPLC radiochromatography. Additional PK studies were performed in the mice and dogs orally given non-radiolabeled TAS-108 or the major metabolite, deEt-TAS-108; employing an LC/MS/MS method for sample analysis.

Results: The TAS-108 plasma concentration time course showed clear dose-dependency. The highest levels of total radioactivity were present 12 hr after dosing in the liver, lungs, ovaries, adrenal, pituitary glands and bone marrow, followed by the level in tumor tissue, however, extremely low amounts were found in the brain. The radioactivity in the tumor was much higher than that in the plasma. Three major metabolites, deEt-, N-oxide-, and 3-hydroxyl-TAS-108, were detected in rat plasma, while only deEt-TAS-108 was detected as the major metabolite in tumor. This N-desethyl form showed potent antagonistic activity toward tumor growth, no agonistic activity toward other tissues, and remained at high levels in the tumor. Oral administration of deEt-TAS-108 to mice and dogs resulted in higher plasma levels, probably resulting from its relative resistance to further metabolism, This might be one reason why deEt-TAS-108 resides in tumor tissue for long period.

Conclusion: The dose-dependency of the TAS-108 PK profile parallels its in vivo anticancer responses. This anticancer activity is probably further enhanced by more pronounced accumulation of deEt-TAS-108, the metabolite exerting a pure antagonistic activity and probably being the sole metabolite so far found in humans. Furthermore, TAS-108 accumulates well in tumor tissues at levels exceeding those observed in plasma.

225 POSTER

Endocrine response after prior treatment with fulvestrant (Faslodex®) in postmenopausal women with advanced breast cancer

K. Cheung, J.F.R. Robertson, N. Scott, R. Owers. *Nottingham City Hospital, Professorial Unit of Surgery, Nottingham, United Kingdom*

Fulvestrant (Faslodex®) is a novel Estrogen Receptor (ER) Downregulator that has demonstrated similar efficacy to the aromatase inhibitor anastrozole in the treatment of postmenopausal women with advanced breast cancer. It remains uncertain whether further response can be achieved with another endocrine agent after prior treatment with fulvestrant.

Among all postmenopausal women with advanced breast cancer who had entered into three phase II/III trials using fulvestrant as second- to fifth-line endocrine therapy in the Nottingham Breast Unit between 1993 and 1999, 27 women who fulfilled the following criteria were studied for their subsequent endocrine response: (1) ER positive or unknown; (2) having been on a subsequent endocrine therapy for at least 6 months and (3) with disease assessable for response according to UICC criteria.

Seven women achieved objective remission/stable disease (OR/SD) at 6 months on fulvestrant with three achieving partial responses (PRs) and four SD. Of these seven women, one had a PR, another had SD and five expe-

rienced progressive disease (PD) at 6 months on subsequent endocrine therapy. Among the remaining 20 women who progressed at 6 months on fulvestrant, there were four with SD and 16 with PD at 6 months on subsequent endocrine therapy. Of these 27 women, 22% (n=6) therefore achieved OR/SD at 6 months of therapy using another (third- to sixth-line) endocrine agent (anastrozole = 4; exemestane = 1, megestrol acetate = 1). It can therefore be concluded that further endocrine response can be induced in a reasonable proportion of women after failure with fulvestrant.

Thursday, 21 March 2002 16:30–18:00

PROFFERED PAPERS

Surgery, including reconstructive surgery

226 ORAL

Efficacy of contralateral prophylactic mastectomy in BRCA1/2 mutation carriers with previous unilateral breast cancer

H. Meijers-Heijboer, M. Menke-Pluymers, C. Seynaeve, W. van Putten, M. Tilanus-Linthorst, E. Crepin, B. ven Geel, C. Brekelmans, J. Klijn.
Erasmus University Medical Center, Family Cancer Clinic, Rotterdam, The Netherlands

Introduction: Unilateral breast cancer (BC) patients with a BRCA1/2 gene mutation have a high risk of contralateral BC and frequently opt for contralateral prophylactic mastectomy (CPM). For this group of patients there are no data on the efficacy of this procedure in reducing the incidence of contralateral BC. Further, the effect on overall survival (OS) is unknown.

Patients and Methods: Included were BRCA1/2 gene mutation carriers with unilateral BC diagnosed after 1-1-1982. Excluded were patients with tumor stage IIIb or higher as well as patients with symptomatic synchronous bilateral BC or previous other invasive cancer. Follow-up started at 1-1-1992 or date of first BC if this was after 1-1-1992. In this way 117 affected carriers were selected, out of which 39 opted for CPM and 78 for surveillance (S). Kaplan-Meier survival curves were used to compare the incidence of contralateral BC between both groups.

Results: Mean age at diagnosis of the primary BC was 40 years (range 30-65) in the CPM group and 41 years (22-73) in the surveillance group (p=0.36). The median duration of follow-up after CPM was 3 years (0.4-9.4); for the surveillance group this was 5.2 years (0.6-9.6). 72% of the CPM group and 38% of the S group opted for prophylactic oophorectomy (PO) (p=0.001). Tumor stage distribution did not differ significantly between the groups. Unexpectedly, tweo invasive breast cancers (3 and 7 mm, resp.) were found at CPM. No incident contralateral BC cases occurred after CPM, whereas 19 cases (24%) of contralateral BC were found in the surveillance group, giving a yearly incidence of 4.3%. This difference was statistically significant (p=0.01). Multivariate analyses, correcting for the effect of PO and adjuvant treatment, on contralateral BC incidence and OS are ungoing and will be presented at the conference.

Conclusion: Contralateral prophylactic mastectomy significantly reduces the occurrence of contralateral BC in BRCA1/2 gene mutation carriers with previous unilateral BC.

227 ORAL

Surgical outcome in patients with nonpalpable breast malignancies detected in a screening program

F.D. Rahusen[1], M.J. Koppe[1], O. Visser[2], J. Benraadt[2], A. Labrie[2], S. Meijer[1]. *[1] Vrije Universiteit Medical Center, Surgical Oncology, Amsterdam, The Netherlands; [2] Comprehensive Cancer Center Amsterdam, IKCA, Amsterdam, The Netherlands*

This study was undertaken to investigate the surgical outcome in patients participating in a national screening program. In view of published guidelines for the management of nonpalpable breast tumors, particular focus of this study was on the use of a preoperative needle biopsy and the number of surgical procedures that patients had to undergo before completion of treatment.

Methods: Patients with nonpalpable breast malignancies detected during a two year screening period were subject of this retrospective study. Mammographic appearance, diagnostic interventions and tumor related variables were assessed in relation to radicality of the first tumor excision, the incidence of residual disease in the re-excision and the total number of surgical interventions.

Results: Of all resected nonpalpable tumors, 101 were pure' DCIS, 141 were invasive cancers with a DCIS component and 141 were invasive only. The presence of microcalcifications on mammography in 184 patients was indicative of the presence of DCIS in 169 resections (92%). The initial operation was a wire guided excision in 376 of 383 included patients. Clear margins were obtained in 58% of all patients. Factors independently related to the radicality of excision were: a preoperative diagnosis ($p = 0.01$), the presence of DCIS ($p = 0.04$) and tumor size ($p = 0.001$). A single surgical procedure was done in 88% of patients with a (pre-)operative histological diagnosis, in 45% of patients with positive cytology and in 13% of patients without a preoperative diagnosis. Residual disease upon re-excision was dependent on margin status ($p < 0.001$), multifocality of the primary tumor ($p = 0.001$) and the presence of DCIS ($p = 0.001$).

Conclusions: A preoperative histological diagnosis will greatly increase the likelihood of a one stage definitive surgical procedure for women with nonpalpable breast cancer. Margin clearance of nonpalpable breast cancer is dependent on both a preoperative diagnosis and primary tumor characteristics. A better compliance with guidelines concerning the use of a preoperative needle biopsy is likely to improve surgical outcome and decrease the number of surgical interventions.

228 ORAL

Ultrasound guided lumpectomy is superior to wire guided resection of nonpalpable breast cancer: a prospective randomised trial

F.D. Rahusen[1], A.J.A. Bremers[1], H.F.J. Fabry[1], A.H.M. Taets van Amerongen[2], S. Meijer[1]. *[1] Vrije Universiteit Medical Center, Surgical Oncology, Amsterdam, The Netherlands; [2] Vrije Universiteit Medical Center, Radiology, Amsterdam, The Netherlands*

The wire guided excision of nonpalpable breast cancer often results in tumor resections with inadequate margins. The use of intraoperative ultrasound (US) is emerging as an alternative guiding tool for the resection of nonpalpable breast tumors. We investigated whether intraoperative US guidance enables a better margin clearance than the wire guided technique in the breast conserving treatment of nonpalpable breast cancers.

Methods: Patients with histologically confirmed nonpalpable breast cancers, that could be visualized with both US and mammography, were randomized to undergo either a wire guided or US guided excision. The US guided procedure was done with a 10Mhz, 3 cm probe in a sterile sheath. Adequate margins were defined as equal or more than 1 mm. Margin clearance, specimen weights and cost-effectiveness of both treatments were compared.

Results: After randomization, 26 patients were to undergo US guided resection and 23 to undergo wire guided resection. One patient underwent US guided excision after a wire dislocation in the operating room. Of 27 US guided excisions, 1 patient (4%) was found to have focally positive margins, 2 patients (7%) had close margins (< 1mm) and 24 patients (89%) had radical margins. Of the wire guided excisions, 4 patients (18%) had positive margins, 6 had close margins (27%) and 12 had radical margins (55%). From the outset radical margins were defined as 1 mm or more. Therefore, the US guided procedure resulted in significantly more patients with radical resections than the wire guided excision: 89% versus 55% respectively [p = 0,007 in chi-square analysis]. Mean tumor size and specimen weight were 1.36 cm and 53 gram respectively in the wire group versus 1,34 cm and 51 gram in the US group. The duration of operation was identical in both groups. The total cost of radiological procedures amounted to 206 Euro for the wire-guided procedure and 65 Euro for the ultrasound guidance.

Conclusions: For ultrasonographically identifiable nonpalpable breast cancer, US guided lumpectomy seems to be superior to wire guided excision with respect to margin clearance and cost-effectiveness. Another advantage of the US guided procedure is that patients do not have to undergo the unpleasant wire placement before surgery.