we have compared the efficacy and toxicity of two different regimens: T 135 mg/m i.v. by a three hours infusion day 1 plus C 75 mg/m day 2 versus Tx 75 mg/m day 1 plus V 20 mg/m days 1 and 5, every three weeks in patients with MBC previously treated with anthracyclines.

Methods: Fron 1/97 to 1/98, 18 evaluable patients entered his study following the usual inclusion and exclusion criterions.

Results:

	T-C	Tx-V
No of evaluable pts.	10	8
No of cycles	45	44
Neutropenia G4 (%)	2 (20)	5 (62)
Febrile Neutropenia (%)	1 (10)	3 (38)
Thrombocytopenia G4 (%)	0	0
Mucositis G3 (%)	0	2 (25)
Peripheral neuropathy (%)	2 (20)	0
CR/PR/SD/PR	2/3/2/3	2/4/1/1
Response Rate	50%	75%

Conclusion: Preliminary results suggest that Tx-V has better activity but with a higher toxicity respect T-C in MBC.

66 POSTER

Liver metastases from breast cancer – Clinical feature and treatment

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We had treated 55 patients with liver metastases of breast cancer at the Osaka Teishin Hospital from 1986 to 1997. In this study, the clinical feature and effect of systemic or intra-arterial chemo-endocrine therapy for these patients were reviewed to clarify characteristics of liver metastases and establish optimum therapy.

Of 55 patients, one patient underwent hepatectomy, 25 were treated with systemic chemo-endocrine therapy such as CAF combination chemotherapy [A], and 10 were treated with one shot intra-arterial chemoenbolization through hepatic artery using Epirubicin and Lipiodol [B], and the other 19 were treated with hepatic arterial infusion chemotherapy using Epirubicin every 2 weeks and continuous infusion of 5-FU [C]. All patients in [B] and [C] were followed by oral chemo-endocrine therapy of MPA alone or MPA + 5'DFUR.

The response rate in the group of [B] and [C] were better than in group [A], whereas there was no significant difference in survival time among three groups. Intra-arterial chemotherapy can prevent hepatic death due to uncontrolled liver metastases in 64.0%(16/25) of cases. The toxicity in the group of intra-arterial chemotherapy ([B] + [C]) was limited.

The thoracico-abdominal lymph nodes metastases was observed in 25.5% (14/55) of cases. In these patients, liver metastases were seemed to be occurred through lymphogenic route. In the group of intra-arterial chemotherapy, the survival time of patients without metastases in the thoracico-abdominal lymph nodes was significantly longer than that of patients with metastases (2-year survival rate was 45.4% vs 0.0%, respectively; $p < 0.01$).

This study suggests that intra-arterial chemotherapy combined with MPA should be safe, effective and useful for the advanced breast cancer patients with liver metastases. But, in cases of *lymphogenic* liver metastases, to prolong survival, it should be required to combine intra-arterial chemotherapy with *more* intensive systemic chemo-endocrine therapy.

Wednesday, 30 September 1998 16:00-18:00

PARALLEL SESSION

New drugs

71 INVITED

New drugs in breast cancer

L. Mauriac. *Institut Bergonié, Regional Cancer Center, Bordeaux, France*

Breast cancer treatments have progressively evolved for 20 years. The most fruitful steps have been marked by the appearance of anthracyclines (with new form of administration) and recently, by the impact of taxanes. These non cross-resistant drugs are used as sequential or alternating single-agents, both administered intensively or in combination. Another way of development is the use of high-dose chemotherapy. Many non randomized trials have been published so far with very promising results. But, there are not yet any randomized phase III studies to confirm the real value of high-dose chemotherapy. Besides these classical approaches, new research is moving. Its goal is to block several growth factors of the cancerous cells through their receptors (tyrosine kinase receptors): epidermal growth factor receptor (EGFR), erb-B2 and the fibroblastic growth factor receptors. The most promising approach seems to be the monoclonal antibody against erb-B2 which has shown a synergistic effect (taxanes). Another means concerns the use of angiogenesis inhibitors, which are presently in early development. The same state is noted for matrix metalloproteinase inhibitors. They are proteolytic enzymes involved in matrix degradation, which favors tumor invasiveness and metastasis. The last two investigational pathways concern telomerase activity inhibitors and gene therapy: we can imagine that a down regulation of gene overexpression (erb-B2) could reverse malignant properties of tumor cells. Hormonal compounds have also recently been developed: new pure antiestrogens and aromatase inhibitors of second and third generation. One of them inhibits the aromatase and blocks the degradation of retinoic acid.

72 ORAL

EORTC 10941; Final results of a phase II study of liarozole fumarate in patients with metastatic breast cancer

J. Klijn, A. Hamilton, L. Beex, L. Mauriac, R. Paridaens, J.A. Roy, A. Awada, A. Van Vreckem, P. Palmer[1], M. Piccart. *On behalf of the EORTC-IDBBC (Investigational Drug Branch for Breast Cancer) participating centres and the [1]Janssen Research Foundation, The Netherlands*

Liarozole is an aromatase inhibitor that inhibits the P450-dependent catabolism of retinoic acid.

Methods: A study of Liarozole was performed from Sep 94 to Apr 98 in 110 postmenopausal patients with MBC belonging to four prospectively defined groups; *1) TAM refractory* ER+, PFS < 1 yr (adj TAM) or <4 mo (TAM for MBC), no prior CT for MBC *2) CT resistant* any ER status, 1–2 prior CT regimens, ≤2 prior HT regimens *3) HT resistant* ER+/?, 1–2 prior HT regimens, PFS ≥ 1 yr for adj HT (ER+), ≥2 yr for adj HT (ER?), ≥4 mo for HT for MBC, no prior CT for MBC *4) ER negative* no prior CT or HT for MBC. Liarozole was administered orally at a dose of 150 mg bid. Dose escalation to 300 mg bid was abandoned in Aug 96.

Results: Toxicity was consistent with retinoid activity: skin, fatigue, nausea/vomiting, stomatitis, alopecia. 4% of patients had possibly related cardiac events. 24% of patients discontinued therapy due to toxicity.

Response	1 n = 16	2 n = 33	3 n = 36	4 n = 25	All patients n = 110
CR (%)	0	0	6	4	3
RR (%)	0	12	17	8	11
Clinical benefit (%)	0	15	25	16	16

Responses were observed in soft tissue, bone, lung and liver. Median duration of response was 11.5 mo (range 2.2–26.8).

Conclusions: Liarozole is an active compound in patients with MBC including those who are not traditional candidates for HT, but it is poorly tolerated by the majority of patients. New analogues of this compound should be investigated.

73 ORAL

Gamma linolenic acid with tamoxifen as primary therapy in breast cancer

F.S. Kenny[1], S. Pinder[2], I.O. Ellis[2], R.P. Bryce[3], J. Hartley[3], J.F.R. Robertson[1]. *[1]Departments of Surgery; [2]Pathology Nottingham City Hospital; [3]Scotia Pharmaceuticals Limited, Stirling, UK*

Purpose: Gamma linolenic acid (GLA) has been proposed as a valuable new cancer treatment having selective anti-tumour properties with negligible systemic toxicity. Proposed mechanisms of action include modulation of steroid receptor structure and function. This is the first study to investigate the effects of GLA combined with hormone therapy in an endocrine sensitive cancer.

Methods: 38 patients with elderly primary (n = 20), locally advanced (n = 14) or metastatic (n = 4) breast cancer consented to take 8 capsules

of oral GLA/day (total = 2.8 gms) in addition to primary tamoxifen. Clinical response (by UICC criteria) was compared with a matched control group on tamoxifen (T) alone (n = 47). Serial tumour core-cut biopsies were taken for immunohistochemical assessment of changes in oestrogen receptor (ER) expression during treatment.

Results: The T + GLA cases achieved significantly faster clinical response (objective response OR vs. static disease SD) than tamoxifen alone, evident as early as 6 weeks on treatment (p = 0.010). T + GLA cases with larger fall in ER at 6 week biopsy had significantly better early response than tamoxifen cases displaying similar degree of ER fall (OR vs. SD 6 wks p = 0.026; 3 mths p = 0.016). These findings suggest that GLA may enhance the therapeutic effects of tamoxifen-induced ER down-regulation to produce a superior clinical response.

Conclusion: Our results propose GLA as a useful adjunct to primary tamoxifen in endocrine sensitive breast cancer, mechanism of action which may involve modulation of ER. Continued follow-up will determine whether this faster initial response will translate into longer ultimate duration of control.

74 ORAL

Breast cancer clinical trials with Faslodex – A new class of antioestrogen

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Purpose: To describe the phase III clinical development of 'Faslodex' (ICI 182,780), a novel steroidal 'pure' (non-agonist) antioestrogen. Faslodex has a unique pharmacological profile, with effects that include potent antitumour activity whilst having no partial agonist activity on the uterus.

Methods: In a phase II study in postmenopausal women (n = 19) with tamoxifen-resistant advanced breast cancer (ABC), 69% of women showed a benefit of 'Faslodex' treatment (partial response or disease stabilisation >6 months) 1 with a median duration of response of 25 months[2]. The phase III programme, currently in progress, includes two large randomised trials, each comparing the efficacy (time to progression; response rate; time to death) and safety of 'Faslodex' versus 'Arimidex' (anastrozole) 1 mg daily in postmenopausal women with ABC having failed previous hormonal treatment. Faslodex is given as a once-monthly i.m injection. Each study will recruit 600 patients. A multinational randomised double blind trial to compare the efficacy and safety of 'Faslodex' with tamoxifen as first-line treatment in postmenopausal women with ABC will be initiated in the near future.

Conclusion: Faslodex has shown good activity in phase II studies. The ongoing clinical programme will define the role of this new pure antioestrogen in the hormonal treatment of ABC. The current status of these trials will be presented.

'Faslodex' and 'Arimidex' are trademarks, the property of Zeneca Ltd

[1] Howell Lancet 1995; 345, 29.
[2] Robertson Breast 1997; 6: 186–189.

75 ORAL

Combination of antimetastatic and antiproliferative therapies in the treatment of experimental breast cancer

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Purpose: High expression of different proteases involved in the metastatic process and neo-angiogenesis appears to be associated with poor clinical outcome. The aim of the present study was to evaluate the antitumor and antimetastatic effects of various protease inhibitors as single agents and in combination with doxorubicin (Dox).

Methods: As experimental model the transplantable rat breast adenocarcinoma (BN 472), that metastasizes to axillary lymph nodes and lungs of Brown Norway rats, was used. The animals were treated during 3 weeks with the metalloproteinase-inhibitor CGS27023A (kindly provided by Novartis), the uPA-inhibitor amiloride and the cytotoxic agent Dox.

Results: As single agents CGS 27023A, amiloride or Dox inhibited s.c. tumor growth with 50–60% as compared with controls ($p < 0.01$). Amiloride ($p < 0.05$) and CGS27023A ($p < 0.01$) added to the antitumor effect caused by Dox. Moreover, all treatments caused a significant decrease of lymph node weight (55–65% inhibition, all $p < 0.01$), and of the number of lung foci ($p < 0.01$). Regarding the number of lung foci, combination treatment of Dox + CGS27023A was more effective than either treatment by itself.

Conclusion: The addition of protease inhibitors to standard antiproliferative agents significantly improved the antitumor effects and decreased the development of metastases. Therefore such combination treatment might be of great value in clinical breast cancer.

76 ORAL

Influence of amifostine (A) on the toxicity and pharmacokinetics (PK) of docetaxel (D) in breast cancer patients: An EORTC-IDBBC study

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D (100 mg/m^2) has been administered as 1st or 2nd line therapy for metastatic breast cancer combined with A (910 mg/m^2) from the second cycle onwards. PK of D have been performed during the first 2 cycles. Clinical data are available for 16 patients (pts) (55 cycles, median number of cycles per patient 4 (2–8) in pts off study and 2$^+$ (2–8)) for all pts. The regimen is very well tolerated with no toxicity related to A and no dose reductions needed. No difference in toxicties was observed between the first 2 cycles (–/+ A) but, in 39 cycles administered with A, the incidence of febrile neutropenia (3% of cycles), skin toxicity (6% of patients) and D related pleural effusion gr 2 (6% of patients) were lower than expected. PK preliminary results suggest that A does not influence D clearance but may interfere with the concentration peak of D. These results warrant a prospective randomized study of D ± A in order to further delineate the potential chemoprotective role of A on D.

77 ORAL

EORTC 10968; Phase I study of Caelyx™ at a six week interval in patients with metastatic breast cancer

A. Hamilton, R. Coleman, L. Mauriac, A. Awada, M. Piccart, A. Van Vreckem, P. Bruning. *On behalf of EORTC-IDBBC (Investigational Drug Branch for Breast Cancer); Institut J. Bordet, IDBBC, Bd de Waterloo 125, 1000 Brussels, Belgium*

Rationale: Caelyx is pegylated liposomal doxorubicin (formerly known as Doxil). It differs from doxorubicin in terms of its prolonged $t_{1/2}$ (>50 hours) and its tendency to accumulate in skin and mucous membranes. Earlier studies at q3W and q4W intervals have demonstrated palmar-plantar erythrodysesthesia as a major toxicity.

Methods: Patients ≥ 70 yo received Caelyx as first line (adj anthracycline mandatory) or second line (no anthracycline for MBC) therapy for MBC. Patients ≥ 70 yo received Caelyx as first or second line therapy for MBC (no prior anthracycline). Caelyx was administered as a 1 hour IV infusion q6W. Neither 5HT antagonists nor steroids were prescribed. Prophylactic mouthwashes were given routinely.

Results: 14 patients have been treated to date (median age 68 (43–78)). *60 mg/m^2*: 8 patients have been treated, 4 of whom have received ≥2 cycles. One DLT has been reported (G3 stomatitis), but toxicity is otherwise mild. One PR has been observed. *70 mg/m^2*: 6 patients have been treated, none of whom has yet received ≥2 cycles. No significant skin or haematological toxicity, alopecia or nausea/vomiting has been noted. Stomatitis is the only significant toxicity and may be dose limiting. One PR has been observed.

Final results will be presented.

78 POSTER

Plasma thrombospondin (pTSP) in early and advanced breast cancer

G.J. Byrne, K.E. Hayden, R. Aggarawal, A. Howell, N.J. Bundred. *Department of Surgery Withington Hospital, Nell Lane Manchester M20 8LR, UK*

Purpose: TSP has been shown to promote metastasis in animal models by increasing adhesion of cancer cells to endothelial cells. We hypothesized that increased production of TSP by breast cancer would be associated with metastases

Methods: TSP was measured in the plasma of women with early breast cancer (EBC) (n = 53), advanced breast cancer (ABC) (n = 60), women who had undergone surgery for breast cancer with no evidence of recurrent