cates that the taxanes are used either before or after other non cross-resistant regimens or drugs, thus widening the application of sequential chemotherapy originally explored with doxorubicin followed by CMF, and suggesting the need for appropriate controls. At this time, trials of adjuvant or preoperative PCT or DCT are performed in "high risk" breast cancer patients. Evidence suggests that patients with over expression of c-erb B2 (HER2) have higher probability of responding to taxanes than patients with HER2-negative tumors. Ongoing studies should explore whether HER2 status, or other factors associated with HER2 and other biologic markers are predictors of efficacy, so that indication of taxane-based therapy could be tailored to specific patient characteristics. Preoperative administration of taxanes represent a unique opportunity to explore such relationships given the rapid and dependable measure of response, and the value of pathologic response to predict long-term results. Finally, the scientific community should carefully explore the relative therapeutic value of PCT and DCT.

S31 Continuous infusional chemotherapy as pre-operative and as adjuvant treatment in early breast cancer

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5-FU is a cycle specific S-phase dependent drug with a short half life of 10–20 minutes. There is therefore a rationale for its use in long term continuous infusional therapy with doses of up to 300 mg/m^2 per day proving feasible for prolonged periods. The schedule is active in patients with heavily pre-treated breast cancer with responses in up to 53% (overall 29%) (*Br J Cancer* 76: 1099, 1997).

At the Royal Marsden Hospital we have evaluated infusional 5-FU 200 mg/2^2 per day for up to 6 months in combination with 3 weekly bolus Epirubicin (E) 60 mg/m^2 and Cisplatin (C) 60 mg/m^2 (infusional ECF) as pre-operative/neoadjuvant treatment in 123 patients with operable breast cancer greater than 3 cm (median 6 cm), initially in a Phase II study of 50 patients and subsequently as part of a randomised Phase III trial. 118 (96%) have achieved objective tumour responses with 67 (57%) achieving CR. The 5 year actuarial survival rate is 78% and the local recurrence rate without associated metastatic disease 12%. The pathological complete remission rate was 16% with a further 5% having residual DCIS only. Pathological CR but not clinical CR is an independent predictor for disease-free survival.

The Royal Marsden is now conducting two multicentre randomised trials of infusional ECF. (i) versus conventional AC (Adriamycin/Cyclophosphamide) as pre-operative/neoadjuvant chemotherapy, with 376 patients so far randomised towards a target of 400; (ii) more recently a similar adjuvant trial versus conventional FEC (5-FU, Epirubicin, Cyclophosphamide), with 168 patients so far randomised. These trials will determine whether encouraging phase II activity with continuous infusional chemotherapy translates eventually into real survival benefit for early breast cancer.

S32 Tailored therapy to equal toxicity: Is it possible?

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The established dose in mg/m^2 for cytostatics is based on a limited patient number in phase I/II. Most cytostatic drugs demonstrate a 3 to 11 fold interindividual variation in clearance/systemic exposure in patients with normal liver and hepatic lab tests. Furthermore, there is no relationship between pharmacokinetic parameters and body surface area. The marked interindividual variation has previously been demonstrated for standard FEC therapy. In the Nordic countries we have an ongoing randomized and controlled study comparing tailored FEC therapy versus standard FEC + high dose therapy with CTCb with bone marrow support. The tailored FEC therapy is given with epirubicin doses from 38 mg/m^2 to 120 mg/m^2 and cyclophosphamide in doses from 450 mg/m^2 to 1800 mg/m^2 combined with a standard 5-FU dose, due to a different toxicity profile. Patients are started on a FEC dose with a 5-FU 600 mg/m^2, epirubicin 75 mg/m^2 and cyclophosphamide 900 mg/m^2 with G-CSF (filgrastim) support and ciprofloxacin prophylaxis. Further dosage escalation or reduction for each course is based on haematological toxicity day 8, 11/12, 15 and 22. The study has included 483 patients October 31, 1997. The results presented here do not interfere with the primary and secondary end-points for the study. We have analysed the first 89 patients, 86 patients completed six or more courses, 83 completed all nine courses. The epirubicin (median 782 mg/m^2) and cyclophosphamide (median 10.330 mg/m^2) doses were significantly higher compared with standard FEC, but with pronounced interindividual variation. The NCI common toxicity criteria revealed similar toxicities for the highest two dose levels compared with the lower dose levels with reference to NCI toxicity 0 or 1 for approximately 2/3 or more of the patients. Our data demonstrate a marked interindividual tolerance of FEC therapy and a marked variation in actually delivered doses, but remarkably similar side-effects.

S33 Anti angiogenesis therapy and strategies

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Tumours cannot grow above 1–2 mm in diameter without developing a new blood supply. The major stimulus for angiogenesis initially may be hypoxia, although inflammation and mutation of p53 are also important. One of the most potent angiogenic factors is vascular endothelial growth factor (VEGF) which is upregulated by hypoxia. We have been studying the role of a hypoxically activated transcription factor, HIF1α in tumour biology and showed expression of the hypoxia signalling pathway in human tumour xenografts using hypoxia response elements coupled to a marker protein. Tirapazamine, was specifically activated in the same cells in which the hypoxia signalling pathway was induced. Investigating VEGF regulation in human breast tumour samples, we found there was a much higher ratio of VEGF protein to RNA than in adjacent normal tissue. This suggests that post-translationally, more protein has been produced for each RNA molecule. We recently completed a phase I clinical trial targeting the VEGF receptor with a staurosporine analogue that inhibits the tyrosine kinase activity of KDR (CG41251). In order to achieve a pharmacodynamic endpoint, surrogate markers were assessed on peripheral blood samples using a whole blood cytokine assay. Various therapy strategies are possible, varying from adjuvant therapy, combination antiangiogenesis therapy with or without chemotherapy, vascular targeting and hypoxia activated drugs, hypoxia-activated or antivascular gene therapy providing major new targets for anti-cancer therapy with a possibility of great selectivity against tumours. Strategies to inhibit angiogenesis include inhibitors of vascular endothelial growth factor, metalloproteinase inhibitors and also heparin analogues. Vascular targeting aims to acutely destroy the already formed tumour vasculature in contrast to anti-angiogenesis which inhibits development of new blood vessels. Drugs that are specifically activated under hypoxia include Tirapazamine and they may be synergistic with either anti-angiogenesis or vascular targeting if there is an increase in hypoxic areas within the tumours. Retroviruses can be selectively targeted to tumour endothelium which is proliferating at up to 50 times higher rate than normal tissue endothelium. Production of pro-drug activation enzymes or anti-angiogenesis cytokines can be used. Which of these is optimum and most practical for the clinic is yet to be determined.

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Friday, February 27, 1998 **16.00–17.00**

Session 9 Adjuvant Systemic Treatments: Cytotoxics and Their Dose

S34 Dose intensity and dose density

M.J. Piccart, L. Biganzoli, A. Di Leo. *Jules Bordet Institute, Brussels, Belgium*

There are at least 5 models allowing the delivery of a higher dose of a cytotoxic drug per unit of time.

Models	Dose per course	Interval between courses	Cumulative dose
I	↑	–	–
II	↑	–	↑
III	↑	–	↓
IV	↓	↓	–
V	–	↓	–

With the support of Hematopoietic Growth Factors (H.G.F.) it is possible to test all these models in the adjuvant setting and to evaluate the impact of a higher dose-intensity on outcome. A review of completed or ongoing adjuvant trials addressing this issue, with a special emphasis on anthracycline-based regimens will be done; the conclusions so far are: 1) a low dose per course can be detrimental 2) an increased dose per course and cumulative dose can be beneficial in high risk patients as far as disease-free-survival 3) dose-densification with H.G.F. support is feasible but has, as yet, no proven advantage 4) careful attention needs to be paid to long-term side effects.