stimulation. This is the first example of a molecular mechanism for tamoxifen stimulated growth.

Raloxifene has been approved by the US FDA for the prevention of osteoporosis but the drug has the added beneficial side effect of preventing breast cancer. This is the first drug to be generally available that reduces the risk of breast cancer in post menopausal women.

S27 Aromatase inhibitors and their role in the adjuvant treatment strategy

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Over the past decade several novel aromastase inhibitors have been introduced into clinical practice. The discovery of these drugs followed on from the observation that the main mechanism of action of aminogluthemide was via inhibition of the enzyme aromatase thereby reducing peripheral levels of oestradiol in post-menopausal patients.

The second generation drug, 4-hydroxyandrostenedione was introduced in 1990 and although its use was limited by its need to be given parenterally it was found to be a well-tolerated form of endocrine therapy.

The third generation inhibitors include Vorozole, Letrozole, Anastrozole and Exemestane, the former three being non-steroidal inhibitors, the latter being a steroidal inhibitor. All these compounds are capable of reducing oestrogen levels to within 5 to 10% of baseline levels compared with 20 to 30% baseline levels in the case of 4-hydroxyandrostenedione.

Studies are currently in progress to determine the value of these third generation aromatase inhibitors in the adjuvant setting. These studies include head-to-head camparison of aromatase inhibitor with Tamoxifen, sequential aromatase inhibitor after Tamoxifen and first-line aromatase inhibitor followed by adjuvant Tamoxifen.

Current issues revolve around the toxicity of these compounds both in terms of effects on the cardiovascular system and bone.

S28 GNRH analogues and ovarian ablation: How to integrate in the adjuvant strategy

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A number of small individual randomized trials, best summarized in the Early Breast Trialists' Cooperative Group Overview, have now clearly shown that ovarian ablation is effective as adjuvant therapy for premenopausal women. Most of these trials compared ovarian ablation to no systemic therapy. There are however, several randomized trials comparing chemotherapy to the same chemotherapy plus ovarian ablation. These trials do not show significantly improved disease-free or improved overall survival for chemotherapy plus ovarian ablation in comparison to chemotherapy alone. The number of women in these trials is small, however.

It has been long appreciated that adjuvant chemotherapy appears more effective in pre than in postmenopausal women. This may relate to dosing and intensity of delivery, but it has been questioned whether part of the mechanism of action of chemotherapy in the premenopausal population relates to its action as a "medical oophorectomy". A number of investigators have analyzed data from randomized trials of adjuvant chemotherapy to see whether patients who developed amenorrhea had an improved outcome in comparison to those who did not. While some investigators suggest that patients who become amenorrhoeic do have improved disease-free or overall survival, other investigators find no such benefit. Now, as increasingly dose intensive and aggressive chemotherapy regimens are given, most premenopausal women will become amenorrhoeic and so this question may become moot.

There are however, currently, several trials ongoing in which patients are being randomized between chemotherapy alone and chemotherapy plus a GNRH analogue. The results of such trials will be greeted with considerable interest. In the meantime it is unclear whether adding ovarian ablation to chemotherapy is of substantial additional benefit. Similarly, it is unclear whether ovarian ablation may substitute for chemotherapy. A few trials in which this has been directly compared suggest that ovarian ablation may be superior in women with high estrogen and/or progesterone receptor levels while chemotherapy may be superior in those with low receptor values. In the setting where one or the other may be considered as an alternative, patient preference concerning the relatively different side effects of these two treatments may be important.

Friday, February 27, 1998 **14.00–15.30**

Session 8 Adjuvant Systemic Treatments: Cytotoxic Strategies

S29 Putting the taxanes to work: Open questions

P.F. Conte, L. Del Mastro. *Dept. Medical Oncology, S. Chiara Hospital, Pisa, Italy*

More than 25 years after the introduction of anthracyclines in the treatment of breast cancer, only few high-power randomized trials have documented the superiority of anthracycline-containing regimens in the adjuvant setting. The slow progress from advanced to early breast cancer was primarily due to the cardiotoxicity of the anthracyclines; however not irrelevant was also the negative results of randomized trials designed to test unrealistic improvements in disease free survival or overall survival. The anthracycline history has clearly shown that a reasonable end point, when comparing two different chemotherapy regimens, is a reduction in the relative risk of relapse or death of less than 10%. Hopefully the ongoing randomized studies aimed to investigate the potential benefit of taxane-containing regimens in the adjuvant setting will have sufficient power to detect small but clinically worthwhile differences. There are however other more specific, unsolved problems which might jeopardize the role of the taxanes. 1. *Schedule and/or pharmacokinetic interferences.* The use of taxol with anthracyclines is complicated by pharmacokinetic interactions which are different according to the schedule of taxol (3 vs 24 hours) and to the anthracycline employed. These pharmacokinetic interactions are probably relevant in terms of cardiotoxicity and might also have pharmacodynamic consequences on cytotoxity. Personal unpublished data on the combination of taxotere/epirubicin have not documented so far pharmacokinetic interactions. 2. *Treatment duration.* Taxanes have been shown to be active also at relatively low doses with mechanism other than direct citotoxicity. In add tion, clinical data in both metastatic breast cancer and ovarian cancer seem indicate a potential delayed activity of these drugs. On these bases the issue of the treatment duration with the use of these drugs in adjuvant setting could be revised. 3. *Interactions with radiotherapy.* Taxanes have been shown to increase the effect of radiotherapy, but this property could be detrimental in early breast cancer. Contemporary use of taxane-containing chemotherapy and radiotherapy may enhance local side effect in patients receiving radiotherapy after conservative surgery. On the other hand the delay of radiotherapy after the chemotherapy completion could reduce its efficacy. 4. *Unexpected long term sequels.* Prolonged use of steroids in adjuvant therapy has been reported to be associated with a higher risk for bone metastases and a small, not statistically significant increased incidence of second malignancies. Some side effects of taxanes, e.g. allergic reactions or fluid retention, are prevented with the use of steroids. Potential adverse effects of this use need to be evaluated. The expected small benefit with the use of new drugs or new strategies in early breast cancer and the advances in early diagnosis with the consequent selection of a better prognosis population prompt a careful evaluation of possible disadvantages and long-term sequels of the use of new treatments.

S30 Putting the taxanes to work

L. Gianni, G. Capri, P. Valagussa, G. Bonadonna. *Istituto Nazionale Tumori, Milan, Italy*

Paclitaxel (PCT) and Docetaxel (DCT) have antitumor activity as good or better than the anthracyclines in women with metastatic breast cancer. Cross-resistance with anthracyclines is at least non complete. Concerns about type I hypersensitivity, more common with PCT, have been discounted based on a large clinical experience showing that incidence and severity of the reactions were decreased and manageable after premedication with corticosteroids and anti-histamines. Onset and severity of the unique dose-dependent fluid retention caused by DCT are delayed and lessened by three-day long administration of corticosteroids. PCT has been tested in many combinations, and has remarkable antitumor activity when infused over 3 hours with bolus doxorubicin (85–95% RR). Preliminary results show similar efficacy of DCT and doxorubicin. The taxanes activity strongly support their use in women with operable breast cancer as adjuvant or primary chemotherapy. Key questions relate to the dose, the combination, the duration of treatment, the timing, and the indication of taxane administration. Adjuvant and preoperative chemotherapy trials employing the taxanes as single agent or in combination with anthracyclines have been started. Their design is taking into account the tolerability of the two drugs, that are used for short periods (usually 4 cycles) in view of the risk of acute and cumulative toxicities (peripheral neuropathy for PCT, cardiotoxicity for PCT and doxorubicin, fluid retention and febrile neutropenia for DCT). This choice impli-

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

I.E. Smith. *Royal Marsden NHS Trust, London, UK*

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?

J. Bergh. *For the SBG 9401 Study. Department of Oncology, University Hospital, Uppsala, Sweden*

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

A.L. Harris. *ICRF Medical Oncology Unit and Molecular Oncology Laboratories, University of Oxford, The Churchill, Headington, Oxford, OX3 7LJ, UK*

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.