XRT either after surgery (the "PROP group" – 760 pts.) or after postoperative adjuvant chemotherapy (the "POP group" – 763 pts.).

Results: Effect of PROP on Local-Regional Disease: 35% of tumors had a clinical complete response (cCR) to PROP and 45%, a clinical partial response (cPR). PROP pts. and pts with responsive tumors were more likely to undergo a LUMP. More pts. whose tumors were ≥5.1 cm underwent a LUMP. PROP resulted in axillary nodal downstaging, and there was a highly significant correlation between tumor response to PROP and pathologic (path.) nodal status. About 25% of pts, with a cCR had no residual tumor on histologic exam of the resected specimen; 11% had only noninvasive intraductal carcinoma, and the rest had invasive tumor on path. exam. *Relation of PROP to Outcome:* Through 6 yrs., outcome of all PROP pts. was virtually identical to that of pts. treated with POP. There was a correlation between breast tumor response to PROP and outcome. The best outcome occurred in pts. whose tumors showed a path. complete response.

Conclusion: Outcome with PROP or POP is similar. A significant correlation exists between breast tumor response to PROP and outcome. PROP increases the use of LUMP, esp. in pts. with large tumors.

S22 Is primary chemotherapy useful in all patients?

S. Scholl, P. Beuzeboc, B. Asselain, J.-Y. Pierga, P. Pouillart. *Institut Curie, Paris, France*

Based on the concept of breast cancer as a systemic disease, the administration of primary chemotherapy was the logical next step, aiming at eradicating micrometastatic disease with the potential to increase cure rates. Yet, published clinical trials testing primary versus adjuvant chemotherapy have shown only minor or no statistical significant benefit. Did we go wrong? The latest update of the Curie trial (S6: 390 pts with an 8 y median follow up) showed a minor survival advantage for the primary chemotherapy group (Wilcoxon 0.09; Breslow 0.05). Clinical response, our surrogate end point, was achieved in 2/3 of all patients and was highly predictive of outcome in our series. It was moreover significantly associated with high S phase and young age. Patients aged <35 years had a higher RR (2.46) for metastatic recurrences despite better response and higher mitotic rates, suggesting that the treatment may have been suboptimal for this subset.

Clinically palpable nodes, high mitotic rates and absence of objective clinical responses were independant predictors for poor survival. Conversely, high risk tumours with high mitotic activity and/or good clinical regression are most likely to benefit from chemotherapy and may benefit from prolonged and intensified therapies. Since response can best be assessed by primary chemotherapy, patients at risk and with highly proliferative tumours (S phase >3%) might best be treated with primary chemotherapy for a minimum of two courses while mdr induction and response can be monitored. Patients with low risk tumors and little mitotic activity as well as patients who do not respond are unlikely to gain from prolonged primary chemotherapy while suffering the discomfort and anxiety as well as the potential for enhanced genetic instability associated with cytotoxics. Following local treatments these patients may become candidates for targeted antibody or vaccine therapies as these become available. Results of a phase I trial directed against MUC1, a vastly overexpressed tumor antigen (detectable in serum as tumor marker CA153) administered in a vaccinia virus carrier showed some promise.

Friday, February 27, 1998 **10.30–12.30**

Session 7 Integrated Therapy: Radiation Therapy/Endocrine Treatment

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S24 How to combine radiation (RT) and systemic (ST) therapies

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Clinical trials have demonstrated both the effectiveness of adjuvant ST and the equivalence of BCT and mastectomy; consequently, clinicians commonly are faced with combining RT and ST following CS. In addition, recent studies have suggested that regional RT after mastectomy and adjuvant CT improves survival. Thus, combining RT and ST has become an issue following mastectomy. The options for combining RT and chemotherapy (CT) are variable. RT and tamoxifen can be delivered concurrently.

Clinical trials are required to resolve this issue. We performed such a trial in which 244 pts at moderate-high risk for relapse (209 were node-positive) were randomized to receive RT before or after 4 cycles of CAMFP. The 5-year failure rates were not different, but the (uncensored) rate of DM was significantly greater in the RT-first arm. However, the risk of local failure was higher in the CT-arm. These results suggest that for pts at moderate-high risk of metastases, it is preferable to give a 12-week course of CT followed by RT. However, 1) it is not certain if this applies to longer courses of CT or to pts at low risk and 2) alternative ways of combining RT and CT which maximize both local and systemic control should be explored. Concurrent full-dose RT and either CMF or dox-containing CT has unacceptable results. We recently completed a study of concurrent full-dose CMF and reduced-dose RT (3960 cGy/22 fx to the whole breast followed by a boost of 1600 cGy/8 fx.) in 105 pts with 0–3 positive nodes with good early results.

In conclusion, the available information regarding combining CT and RT is limited and often conflicting. Differences in the details of the treatment (surgery, RT, and CT) may be factors. In the meantime, clinicians might modify the sequence in individual patients based on the patient's risk of metastases and the margins of resection.

S25 Novel approaches using radiation techniques

Lars E. Rutqvist. *Karolinska Hospital, Stockholm, Sweden*

New information has recently emerged concerning the role of adequate local control of breast cancer through the use of postoperative locoregional therapy in conjunction with adjuvant cytotoxic chemotherapy. The updates of the Danish DBCG 82b trail and the British Columbia Trial have confirmed a significant overall survival benefit with postoperative radiation therapy in patients with high-risk disease. These trials together with in-depth analyses of previous studies suggest that the mechanism of the survival benefit is eradication of subclinical locoregional deposits of tumour cells with a potential for further dissemination if left untreated. Despite these findings several questions remain largely unanswered concerning the optimal way to integrate radiation therapy into routing clinical practice. For instance, which subgroups are likely to benefit from comprehensive treatment including the peripheral lymphatics as opposed to treatment of the breast/chest wall alone? Until results are available from future controlled trails the Stockholm Breast Cancer Group has adopted a provisional policy of offering locoregional radiation therapy to subgroups of patients whose 10-year cumulative risk of local failure (in the postmastectomy setting) in the absence of radiation exceeds 15–20%. On the basis of results from the Stockholm Breast Cancer Data Base including c. 3,200 patients treated with surgery alone or surgery plus adjuvant chemotherapy, cumulative risks of this magnitude concern all patients with 4 or more positive axillary nodes, but also subgroups of patients with node-negative disease or 1–3 positive nodes in case of a large histopathological tumour size (>20–30 mm) or a high proliferative activity. The available randomized trails and overviews have convincingly demonstrated that it is essential to minimize long-term radiation side effects in the myocardium in order to achieve an overall survival benefit. Such effects are positively correlated with the cardiac dose-volume. An adequate treatment technique is therefore essential, particularly if the internal mammary nodes are included in the target. Individual treatment planning should be encouraged since some patients have an "unfavorable anatomy" with the heart located anteriorly in the mediastinum. Such patients may receive a high cardiac dose-volume even with conventional tangential field irradiation that does not include the internal mammary nodes. In summary, recent information highlights the fact that radiation therapy plays an important part in the primary management of many breast cancer patients. However, an adequate treatment technique that minimizes the risk of late cardiac effects is paramount in order not to compromise the potential treatment benefit in terms of overall survival.

S26 The molecular biology of the estrogen receptor (ER) aids in the understanding of tamoxifen resistance and breast cancer prevention with raloxifene

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The recent crystallization of the ER with estradiol or the new antiestrogen raloxifene has provided an invaluable insight into drug resistance to tamoxifen (Brzozowski et al Nature 389:753–759, 1997). Tamoxifen can stimulate the growth of both breast and endometrial tumors in the laboratories. One theory to explain this phenomenon is mutation of the ER. However, there is only evidence for one natural mutation (Wolf and Jordan Breast Cancer Res. Treat 31:129–138, 1994). Aspartate 351 is changed to tyrosine and the mutant ER increases the estrogenicity of raloxifene (Levenson et al J. Steroid Biochem Mol. Biol. 60:261–268, 1997). It has been known for forty years that a correctly positioned aminoethoxy side chain is essential for antiestrogen action. Now we know from the crystal structive of the ER raloxifene complex that the side chain must interact with aspartate 351 to produce the conformational change in the ER that blocks estrogen action. Amino acid 351 is the key to antiestrogenic activity; a mutation prevents the change in conformation resulting in estrogenic

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

R.C. Coombes. *Department of Cancer Medicine, Division of Medicine, Imperial College School of Medicine, Charing Cross Hospital, Fulham Palace Road, London W8 8RF, UK*

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-