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

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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-