proliferation with anastrozole compared with tamoxifen or anastrozole and tamoxifen combined.

**24** INVITED

**Towards optimisation of chemotherapy**

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Preoperative or neoadjuvant (primary systemic therapy, PST) was used in the past to treat inoperable and inflammatory BC. The NSABP-B 18 study showed survival equivalence between preoperative and postoperative (adjuvant) chemotherapy and a strong correlation of disease free and overall survival with pathological complete remission (pCR). In order to achieve higher pCR rates, different strategies are applied: use of Taxanes, modification of dose, number of cycles and density and use of targeted new therapies. The role of Taxanes was investigated in several trials: NSABP B-27 showed a pCR rate of 25.6 after 4× AC followed by 4× Docetaxel. In the ECTO-trial pCR was 23.8% after 4× Adriamycin–Paclitaxel and 4× CMF. We evaluated dose-density and dose intensity of Paclitaxel (P) and Epirubicin (E) in 678 patients with a median diameter of 4 cm or inflammatory disease. There was a statistically significant increase in the rates of measurable response, pCR as well as negative axillary lymphnodes at surgery in the dose-dense compared to standard EP. Consecutively, the rate of breast conserving therapy (BCT) was significantly higher in this arm. With P weekly for 12 weeks followed by 4 cycles of FAC q 3w pCR could be increased to 29%. In the ongoing randomised multicenter AGO study PREPARE (preoperative Epirubicin–Paclitaxel–Aranesp) a dose-dense therapy is compared to standard doses and intervalls with or without Darbepoetin alpha. The total treatment duration in both arms is 24 weeks. Patients with Her2 neu amplification are eligible for the AGO TECHNO (Taxol–Epirubicin–Cyclophosphamide–Neoadjuvant) trial, an open phase II study with EC, then P and Herceptin before surgery followed by Herceptin for 9 months after surgery. Complete resection of the tumor – including non-invasive areas – should be achieved. Therefore, surgery remains a key element of breast cancer therapy after PST. The rate of breast conservation is significantly higher after primary systemic therapy compared to primary surgery. Reports from NSABP B-18 at 10 years and ECTO at 24 months show that the ipsilateral breast tumor recurrence is not increased, regardless of the type of surgical treatment performed (mastectomy vs BCT) and initial tumor size. The results of these studies could be an important progress in answering questions about optimising breast cancer therapy. One of the major advantages of PST is the inclusion of innovative predictive markers from the primary tumor like gene profiles to allow more tailored therapy, since response to therapy can be evaluated within 6 months after diagnosis.

**25** INVITED

**Challenges for local treatment**

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Primary (or pre-operative chemotherapy, POC) in large sized but operable breast cancer (T2–3, N1–2) represents an alternative to the classical surgical approach. The National Cancer Institute of Milan was one of the first Institutions where this approach was investigated and applied from the beginning of the 1980s. The objective is to avoid mastectomy in patients otherwise candidates for demolitive surgery. A second line objective is to reduce local relapse and mortality in this subset of patients.

After 20 year experience and about 1000 patients treated we can summarise the most important findings as follows:

1. Pre-operative chemotherapy is effective in reducing the size of primary tumour allowing an high rate of breast conservative treatment (BCT).
2. This reduction can be observed in each sub-group of tumours regardless the size.
3. Similar results can be observed in axillary nodes with an increasing rate of negative nodes in case of POC in tumours of the same size.
4. POC in a high percentage of cases leads to a re-staging (down staging) of the disease.
5. Local control of the disease can be guaranteed considering that the observed rate of local relapse in case of BCT was 6.8% at eight years.

These promising results open a new challenge for breast conservative surgery that should be adopted with some different modalities compared to the classical approach. Main surgical problems following POC before planning BCT include: clinical evaluation of tumour regression, significance of persistant microcalcifications, identification of the original tumour site, reliability of gross evaluation of residual mass, clear resection margins, reliability of frozen sections.

Some tools to overcome these difficulties can be suggested.

a. Mammography is the best way to assess tumour regression;
b. to tattoo the skin projection of the tumour borders before starting chemotherapy, is the best way to recognize the correct size of the primary tumour in case of total regression;
c. diffuse microcalcifications should be considered as a contraindication to POC for BCT. Microcalcifications very rarely disappear at the end of chemotherapy;
d. frozen sections should be avoided whenever possible and clear margins should be assessed considering "free of disease" every breast tissue in which cancer can not be actually demonstrated. This means that necrosis and/or fibrosis in the site where cancer was present before chemotherapy should be considered healthy tissue. Margins assessment can be properly performed with the technique of "cavity shaving".

When BCT can not be performed, a skin sparing radical mastectomy with immediate reconstruction can be carried out in the majority of cases.

Sentinel node biopsy, according to different experience reported, can be adopted for mapping axillary nodes. This technique is particularly appropriate in case of complete or significant regression of the primary tumour.

## Wednesday, 17 March 2004 14:15–15:45

**SYMPOSIUM**

# New targets for breast cancer therapy

**26** INVITED

**Receptor targeted therapies**

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A variety of new approaches that target signal transduction pathways involved in angiogenesis, metastasis, and apoptosis are in clinical development in breast cancer. Among these new agents, there is an increasing number of them that are being designed to target tyrosine kinase receptors and their growth factors. The rationale for this approach is compelling as receptor tyrosine kinases have been found to be abnormally activated in breast cancer. There are close to 60 transmembrane receptor tyrosine kinases distributed in 20 subfamilies based upon the ligands they recognize, the biological responses they induce, and according to their primary structures. Examples of receptors that play a role in breast cancer include the epidermal growth factor receptor family, the insulin-like receptor, the transforming growth factor beta receptor family and the vascular endothelial growth factor receptor (VEGFR) family. The epidermal growth factor (EGF) family of growth factors consists of at least ten different members that bind and activate four receptors, namely ErbB1 (EGF receptor), ErbB2 (HER2/Neu), ErbB3 and ErbB4. Binding of EGF family ligands to ErbB receptors induces receptor activation by both homodimerization and heterodimerization, thus generating a complex array of combinatorial signals leading to proliferation and other cellular activities. There is a plethora of compounds that target these receptors including anti-ErbB1 and anti-ErbB2 receptor monoclonal antibodies and tirosine kinase inhbitors of the ErbB1, ErbB2 and ErbB4 receptors. Among the antibodies, the anti-ErbB2 receptor antibody trastuzumab is active in ErbB2-amplified tumors and is currently undergoing evaluation in the adjuvant and neoadjuvant setting. Another antibody against ErbB2, rhuMAb 2C4, prevents receptor heterodimerization and is currently under evaluation in clinical trials. In terms of low-molecular weight tyrosine kinase inhibitors, activity has been reported with an anti-ErbB2 inhibitor, in patients with ErbB2 overexpressing tumors that had progressed on trastuzumab therapy. In addition to anti-ErbB therapies, there are a series of clinical trials with anti-agiogeneis agents. The rationale stems from several studies that have shown a correlation between the degree of vascularization of the tumor and prognosis. Quantitation of microvessel in histologic specimens of invasive breast cancer, for example, has provided an indication of the risk of developing metastasis. About 20 angiogenesis inhibitors are currently being tested in human trials. Agents directed at the VEGF pathway that are currently under evaluation in breast cancer include monoclonal antibodies targeting VEGF, VEGFR (anti-Flk-1 antibody), and synthetic small molecule receptor tyrosine kinase inhibitors.