Meeting report

5th Milan Breast Cancer Conference, Milan, Italy, 11–13 June 2003

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Introduction

In just a few years the Milan Breast Cancer Conference (the 5th of which was held from 11 to 13 June this year) has become an important forum at which advances in breast cancer research and patient care are reviewed in a multidisciplinary manner. More than 850 physicians (breast surgeons, epidemiologists, clinical oncologists, radiotherapists, pathologists, radiologists) from nearly 55 countries attended the meeting.

The conference was guided to a successful conclusion by the experience of the chairmen Dr Umberto Veronessi and Dr Aaron Goldhirsch. This year the European Institute of Oncology Award was given to Dr David Page, Professor at Vanderbilt University Medical School, who gave an excellent lecture outlining the importance of ductal carcinoma *in situ* as a local precursor of invasive cancer, and the lesions related to *in situ* staging.

Prevention and detection in high risk women

Management of high risk women is a major topic. Therefore, the first section of the conference was dedicated to prevention and detection. The main points were summarized in a plenary session. Jack Cuzick (Imperial Cancer Research, UK) gave an overview of the risk factors, which can be divided into four groups: family history/genetic; reproductive/hormonal; proliferative benign breast disease; and mammographic density. Less is known about the possible interactions between these factors. However, a computer program able to synthesize the factors into an individual risk profile could conduct an assessment.

Following this broad definition of high risk, Judy Garber (Dana Faber Cancer Institute, Boston, MA, USA) showed that *BRCA* mutations are the cause of breast cancer in only 5–10% of the total cases. In addition, *BRCA* mutation carriers have a 40–60% risk for developing contralateral breast cancer. Julian Peto (Institute of Cancer Research, Sutton, UK) emphasized the importance of reproductive factors in breast cancer.

In chemoprevention Andrea Decensi (European Institute of Oncology) and Lawrence Wickerham (Associate Chairman of the National Surgical Adjuvant Breast and Bowel Project) showed that the use of tamoxifen can reduce the incidence of oestrogen receptor (ER) positive breast cancer by up to 50%; however, the effect of tamoxifen in ER negative breast cancer is unknown. The dosage of tamoxifen, and the concomitant use of hormone replacement therapy and tamoxifen 5 mg/day will be evaluated in the Hormone Replacement Therapy and Tamoxifen (HOT) study. The Study of Tamoxifen and Raloxifene (STAR) trial, co-ordinated by the National Surgical Adjuvant Breast and Bowel Project, will compare tamoxifen 20 mg/day with raloxifene 60 mg/day, both for 5 years; the data can be reviewed online (http://www.breastcancerprevention.com).

Surveillance plays an important role in high risk patients, and Giorgio Rizzatto (Ospedale Civile di Gorizia, Italy) described the importance of ultrasound in breast cancer while confirming that the 'gold standard' is still mammography. In this context, Enrico Cassano (European Institute of Oncology) explained that the benefit to women from mammographic screening from ages 50 to 75 years exceeds the risk associated with radiation exposure by a factor of almost 100 [1]. It is also important to give consideration to breast density because high density can obscure the presence of some lesions. Sylvia H Heywang-Koebrunner (Martin-Luther University, Halle, Germany) provided preliminary data indicating that magnetic resonance imaging (MRI) can detect breast cancers that are not visualized by mammography or ultrasound. Thus, it

 ER = oestrogen receptor; MRI = magnetic resonance imaging; SNB = sentinel node biopsy.

appears that MRI may allow an increase in sensitivity to in excess of 90%. MRI promises to improve diagnosis, but studies are needed to confirm that use of MRI confers survival advantages and to further reduce the incidence of false-positive findings.

New technologies are always being developed, and in the near future these will lead to improved diagnosis. An example is the Biofield Diagnostic System (Biofield Corp., Alpharetta, GA, USA), which quantifies cell proliferation by measuring electrical potentials at the skin surface. Angiogenesis in breast tissue may be identified via infrared imaging using the DOBI system (DOBI Medical Systems, Mahwah, NJ, USA) and the BioLuminate Diagnostic System (Bioluminate Inc., Dublin, CA, USA), which is a device that aims to differentiate cancerous lesions from normal tissue and display the information in real time on a computer screen. These technological advances were described by Wolfgang Gatzemeier (Fondazione S Maugeri, Pavia, Italy).

Live surgery

Surgery was demonstrated in three different operating theatres. Mattia Intra (European Institute of Oncology) coordinated communication between the operating rooms and the audience. In the first theatre, Professor Umberto Veronesi showed the technique of nipple sparing mastectomy plus intraoperative radiotherapy. In the other two theatres Drs Gennari and Galimberti demonstrated the Radioguided Occult Lesion Localization (ROLL) technique, sentinel node biopsy (SNB) and internal mammary node dissection.

Pathology

Following the live surgery section, Ian O Ellis (City Hospital, Nottingham, UK) outlined some important issues of clinical relevance, including the traditional prognostic factors. The TNM International Union Against Cancer classification fails to provide a useful tool for therapeutic decision making. Therefore, Giuseppe Viale (European Institute of Oncology) suggested other features, such as endocrine responsiveness or presence of special histology findings, that may lead to modification of the current staging system.

Sentinel node in breast cancer

According to Viviana Galimberti (European Institute of Oncology) and to data obtained in the Milan trial, no difference exists between total axillary clearance and SNB findings, indicating that the latter procedure is as effective as the traditional method in screening for metastasis to the axilla. However, in the International Breast Cancer Study Group 23-01 trial (designed to determine the most appropriate treatment when micrometastases are present in the lymphatic node), no significant results have yet been obtained – the trial requires more patients. Paolo Veronesi (European Institute of Oncology) explained the prognostic significance of the internal mammary node, which was complemented by a description of the role of the pathologist by Donald Weaver (University of Vermont College of Medicine, Burlington, USA) who suggested that, ideally, the node should be sectioned into 2 mm slices.

Omgo Nieweg (Antoni Leeuwenhoek Huis, Amsterdam, The Netherlands), David Nielsen Krag (University of Vermont College of Medicine, Burlington, USA) and Gordon Schwartz (The Breast Health Institute, Philadelphia, USA) provided an overview of the implementation of SNB, which requires complete training of a team comprising surgeon, pathologist and nuclear medicine physician. Intense training is required to accomplish effective results and to achieve low percentages of false-positive and false-negative cases.

Dr Jean Yves Petit (European Institute of Oncology) gave a lecture covering the indications for nipple sparing mastectomy and the importance of the tissue beneath the nipple–areola complex (which should be approximately 2 cm thick to avoid necrosis), and outlining the potential utility of transoperative radiotherapy with a dosage of 16 Gy.

Electron intraoperative therapy, targeted intraoperative radiotherapy and bachytherapy

In the first lecture of this section, Umberto Veronesi (European Institute of Oncology) emphasized the importance of immediate radiotherapy during breast conserving surgery. The objective of intraoperative radiotherapy is to deliver higher doses to the target area while surgically displacing dose limiting structures. Electron intraoperative therapy can be used not only to boost radiation dose but also to provide a full treatment dose in a breast conserving approach to treatment. In the literature there is no difference in results between diverse treatment trials; we were also reminded that, although radiotherapy reduces local recurrence by threefold (as compared with groups with no radiotherapy), the survival rates do not differ. The European Institute is currently undertaking a trial in which patients in one arm will receive postsurgical radiotherapy at a dose of 50 + 10 Gy and those in the other will receive only intraoperative radiotherapy at a dose of 21 Gy. No data have yet been reported.

Roberto Orecchia (European Institute of Oncology) stated that local recurrence after breast conserving surgery occurs mostly in the quadrant harbouring the primary carcinoma. Electron intraoperative therapy is given by a mobile linear accelerator with a robotic arm delivering electron beams that can produce energies from 3 to 9 MeV. This device can be positioned in an operating theatre. At present, various dose levels (10–21 Gy) are being tested in early stage breast cancer patients, without

significant side effects [2]. Targeted intraoperative radiotherapy is another option in this field, with acceptable cosmetic outcome according to Jayant S Vaidya (University College, London, UK).

MammoSite (Proxima Therapeutics, Alpharetta, GA, USA) is a newly developed device for brachytherapy, which delivers an accelerated dose of radiation to a well defined area of the breast. The indications (with respect to age, nodal status, metastases status) are under revision. With this device the dose administered is 34 Gy but only within 1 cm around the device. After application of MammoSite, the device can be controlled by ultrasound. The device should be removed 72 hours after the last irradiation.

Neoadjuvant therapy

Neoadjuvant therapy has been routinely administered to women with locally advanced breast cancer since 1980. Eric P Winer (Dana Farber Cancer Institue, Boston, USA) suggested that new regimens and better tailoring of treatment are needed, for example addition of non-cross-resistant agents or biological agents. Several studies [3] have demonstrated that preoperative and standard adjuvant chemotherapy are equivalent with respect to disease-free and overall survival. Also, preoperative treatments lead to a lesser surgical procedure, and the response and biological parameters can be monitored. Recent pilot studies using trastuzumab in the preoperative setting have yielded promising preliminary results [4].

The use of predictive factors allows more effective use of available therapies by enabling clinicians to distinguish between patients who are likely to obtain substantial benefit from treatment and those in whom the same therapy is less likely to be effective [3]. Thus, identification of predictors of response is an important goal. According to Marco Colleoni (European Institute of Oncology), the factors that are associated with pathological complete response were the absence of ER and progesterone receptor expression, high grade and elevated Ki-67. Information on endocrine responsiveness before primary systemic therapy will lead to better tailoring of treatment modalities, thus increasing the benefit of chemotherapy in chemotherapy sensitive tumours and focusing on hormonal approaches in groups in which primary endocrine therapy could be useful.

Aromatase inhibitors and beyond

Richard J Santen (University of Virginia Health System, Charlottesville, USA) summarized the current status and the future of aromatase inhibitors. The main difference between tamoxifen and aromatase inhibitors lies in their sites of action. Although tamoxifen acts by blocking cell proliferation due to the effect of oestrogens, oestrogen metabolites continue to exert their affects on breast cells. On the other hand, aromatase inhibitors act by blocking the conversion of androgens to oestrogen, avoiding the formation of oestrogenic metabolites. The safety profile of aromatase inhibitors differs from that of tamoxifen. Aromatase inhibitors increase the risk for bone loss and the fracture rate; tamoxifen results in increased risk for endometrial cancer and venothrombotic episodes. So, the future of aromatase inhibitors may be in the area of breast cancer prevention. Eric Paul Winer (Dana Farber Cancer Institute, Boston, USA) discussed data from the Arimidex and Tamoxifen: Alone or in Combination (ATAC) trial [5]. In that study, over a median follow-up period of 47 months, the disease-free survival was statistically different between the groups, favouring the aromatase inhibitor group. The only disadvantage of aromatase inhibitors is that their long-term toxicity is unknown. Toremifene, fulvestrant and goserelin should be studied more intensively, according to Monica Castiglione-Gertsch (Swiss Association of Research against Cancer/International Breast Cancer Study Group, Bern, Switzerland).

New cytotoxic drugs

The development of new cytotoxic drugs concerns all clinical oncologists. Diverse compounds have been developed and are in phase I trials to define the maximum tolerated dose; the next step will be phase II trials. Compounds such as LY355703 (synthetic derivative of marine cryptophycins) induce mitotic arrest by binding at the microtubule vinca-binding domain. Also, according to Cristiana Sessa (Ospedale San Giovanni, Bellinzona, Switzerland), the dosages for RPR 109881A and BMS 184476 (paclitaxel analogues) for evaluation in phase II trials have already been defined. Angelo di Leo (Institut Jules Bordet, Brussels, Belgium) indicated that the strategy for developing new cytotoxic compounds should be modified because these agents will play a major role in endocrine resistant disease, and this will depend on HER-2 status.

Molecular targeted compounds

The epidermal growth factor receptor family of proto-oncogenes is known to be clinically relevant to a variety of human malignancies. This gene family encodes four structurally related transmembrane receptor tyrosine kinases, namely HER-1, HER-2, HER-3 and HER-4. Clinical trials of HER-1 and HER-2 inhibitors are ongoing. Combination treatment with carboplatin, pacltaxel and trastuzumab (a monoclonal antibody that targets cancer cells that overexpress HER-2) is well tolerated weekly, as it is with administration every 3 weeks. According to Guiseppe Curigliano (European Institute of Oncology, Milan, Italy), abnormalities in growth factor signalling pathways may account for the endocrine-resistant phenotype in breast cancer, and may involve the activation of specific cross-talk between ER and other pathways. There appear to be different levels at which this cross-talk may occur, including epidermal growth factor receptor, which may become downregulated during endocrine treatment.

George W Sledge (Indiana University Medical Center, Indianapolis, USA) gave the closing lecture on the subject of angiogenesis and antiangiogenesis. Angiogenesis plays a central role in both local tumour growth and distant metastasis. Thus, the inhibition of angiogenesis offers an attractive therapeutic target with little expected toxicity. Because of the low mutation rate of genetically stable endothelial cells, antiangiogenic therapy was initially thought to be 'resistant to resistance'. However, resistance mechanisms to antiangiogenic therapy have now been identified, including endothelial cell heterogeneity and tumour cell heterogeneity. Tumour growth (or regrowth) may occur independent of angiogenesis.

Conclusion

Success in breast cancer management depends on the development of new diagnostic methods, surgical treatments, histopathological compliance and, of course, new treatment options. The Milan Breast Cancer Conference met its objective – to evaluate breast cancer with the latest technologies in a multidisciplinary manner. It can now be considered a reference point in breast cancer management.

Competing interests

None declared.

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