Meeting report

The 6th Milan Breast Cancer Conference, Milan, Italy, 16–18 June 2004

Roberto Gennari, Saverio Cinieri, Marco Colleoni, Stefano Zurrida, Aron Goldhirsch and Umberto Veronesi

European Institute of Oncology, Milano, Italy

Corresponding author: Stefano Zurrida, stefano.zurrida@ieo.it

Published: 14 October 2004

Breast Cancer Res 2005, **7**:E1 (DOI 10.1186/bcr943)
© 2004 BioMed Central Ltd

Abstract

The 6th Milan Breast Cancer Conference, held in Milan, Italy, over 16–18 June 2004, was attended by more than 1000 physicians from 60 countries. This report summarizes the highlights of the most interesting conference presentations on selected topics.

Keywords: breast cancer, chemoprevention, chemotherapy, intraoperative radiotherapy, sentinel node biopsy

Introduction

Breast cancer detection and staging are constantly evolving as technologies improve. Breast cancer surgery is also undergoing continuous refinement, with the objective being to achieve optimal cosmetic results. Surgery has been combined with intraoperative radiation therapy to achieve the best local disease control with minimal side effects. Presentations at the Conference focused on recent advances in techniques for sentinel node biopsy (SNB). Patient preferences are an essential component of treatment decision making, leading to improved quality of life and patient satisfaction. The response to preoperative systemic treatment can be used to tailor treatment to individual patients. Finally, there is a need to identify the optimal sequence of endocrine therapies in the adjuvant setting.

Researchers and clinicians at the Milan meeting have made important contributions to advances in medical therapies. This meeting report provides a brief presentation on some of these developments, with the objective being to stimulate ideas regarding what should be done tomorrow.

Regional lymph node mapping

Monica Morrow (Northwestern Memorial Hospital, Chicago, IL, USA) presented indications and contra-indications to SNB. She observed that clinical experience with lymphatic mapping and SNB has defined populations in which the technique is likely to be safe and accurate. At the consensus conference in 2001, contraindications to SNB were reported to be clinically positive lymph nodes; locally advanced breast cancer, before or after neoadjuvant therapy; pregnancy or lactation; and prior axillary surgery [1]. Since that time data have been reported that indicate that SNB can be performed after neoadjuvant therapy in patients without locally advanced breast cancer, and that the technique is appropriate for those with multicentric carcinoma [2]. Similar findings regarding the accuracy of axillary SNB after neoadjuvant chemotherapy were presented by Schwartz (The Breast Health Institute, Philadelphia, PA, USA). In fact, Schwartz and colleagues have abandoned complete (levels I and II) axillary dissection in patients undergoing induction chemotherapy whose axillae are considered clinically negative following their chemotherapy, irrespective of node status prior to neoadjuvant treatment. Morrow discussed concerns regarding the clinical implications of a false-negative SNB. This issue was addressed with the publication of follow-up data on 4551 patients who underwent SNB alone, with only five (0.001%) isolated axillary recurrences. Randomized trials have demonstrated that morbidity after SNB is significantly less than after axillary dissection, both in the immediate postoperative period and during 2 years of follow up.

BCT = breast conserving therapy; RT = radiotherapy; SNB = sentinel node biopsy.

Umberto Veronesi (European Institute of Oncology, Milano, Italy) reported on the first series (376 patients) in which the first node draining the tumour area was identified in 99% with the use of a radiotracer (^{99}Tc) and gamma detector during surgery. All patients underwent complete axillary dissection. The study found an overall accuracy of 96.8%, a sensitivity of 93.3% and a specificity of 100%. Veronesi also updated the findings of the Milano trial on axillary SNB. Between 1998 and 1999, 516 patients were randomized in a controlled study comparing SNB and immediate axillary dissection versus SNB and dissection only in those cases with a positive SNB. The average follow up in the study is 5 years, and there are no differences between the two arms of the study in local or axillary recurrences, distant metastases and overall survival [3].

Since 1999, SNB has been offered as a standard of care to all European Institute of Oncology breast cancer patients. More than 7000 women underwent SNB, and recent data revealed that there were fewer local recurrence than expected. Armando Giuliano (John Wayne Cancer Institute, Santa Monica, CA, USA) discussed the current status of sentinel node dissection in the USA. He observed that SNB had already become the preferred management option for patients with clinically negative lymph nodes at most breast cancer centres in the country. The procedure was rapidly accepted because it is a diagnostic procedure with high positive and negative predictive values, and low morbidity. Currently, patients with early breast cancer who are clinically node negative are managed with SNB; also, in most centres, if the sentinel node is tumour free, then axillary lymph node dissection is not performed.

From the discussion, several factors were associated with failure to identify a sentinel node: surgeon inexperience, older age and obesity. Other than surgeon inexperience, no factor has been identified that reliably predicts the likelihood of a false-negative sentinel node.

Viviana Galimberti (European institute of Oncology, Milano, Italy) reported that micrometastases (< 2 mm) are found more frequently by extensive pathological examination of the sentinel node. In order to evaluate the requirement for axillary surgery, patients with breast cancer up to 3 cm with clinically negative axillae and found by SNB to have only micrometastases were recruited and randomly assigned either to complete axillary dissection or to no further axillary treatment. The primary end-point of the trial is disease-free survival. Thus far, about 250 patients have been recruited.

On aggregate, the data discussed in this session of the meeting indicated that SNB is the preferred technique for axillary staging in the majority of patients with stage I and II breast cancer.

Partial breast irradiation

One of the 'hot topics' of the meeting was covered by the session on partial irradiation of the breast [4]. From the panel, the message was clear that, over the past decade, breast conserving therapy (BCT) has become an important option for patients with breast cancer; this is because long-term disease free and overall survival rates for BCT and radical surgery are similar. The current standard of care for early operable breast cancer is quadrantectomy or lumpectomy and a 5- to 7-week course of whole-breast postoperative radiotherapy (RT). It is possible to reduce treatment time by confining RT to the tumour bed. Based on the hypothesis that it is sufficient to just treat the index quadrant with RT, Roberto Orecchia (European Institute of Oncology, Milano, Italy) described a new technique for intraoperative RT using a single dose of radiation delivered directly to the tumour bed. A mobile linear accelerator with a robotic arm is utilized that delivers an electron beam to produce energy ranging from 3 to 9 MeV. A single dose of 21 Gy was demonstrated to be equivalent to 60 Gy delivered in 30 fractions at 2 Gy/fraction. Through a perspex applicator, radiation is delivered directly to the mammary gland in order to spare the skin. To protect the thoracic wall, an aluminium–lead disc is placed between the gland and the pectoralis muscle [5]. More than 600 patients have been randomized into a trial comparing this new technique (electron intraoperative therapy) with standard external RT. At this time there is no statistically significant difference in local relapse rates between the two arms.

Another randomized study was also presented by Jayant Vajdya (University College London, London, UK), who tested single dose treatment using low energy X rays (Intrabeam™; Photoelectron Corporation, Lexington, MA, USA) targeted at peritumoural tissues from within the breast. The technique employs a miniature electron-beam driven X-ray source that emits 'soft' X rays (50 kV). Rapid attenuation of radiation within tissues occurs, and so the dose is inversely proportional to the third power of the distance between target and source, thus reducing the damage to surrounding normal tissues and minimizing the need for radiation protection for operating personnel. In patients with small breast cancers, this could be the sole treatment. A randomized trial (Targeted Intraoperative Radiotherapy; TARGIT) is under way in the UK, Europe, USA and Australia. Preliminary results indicate that this technique has the potential to reduce local recurrence by avoiding geographical misses and achieving excellent dosimetry, replacing 6 weeks of postoperative RT in those patients who are at low risk for local recurrence.

Roberto Gennari (European Institute of Oncology, Milano, Italy) presented data on a new breast treatment device (Mammosite RTS™; Proxima Therapeutics Inc., Alpharetta, GA, USA) that was recently developed [6]. This device

delivers a high-dose-rate source at the centre of an inflatable balloon that is placed in the surgical cavity at the time of BCT. This new device consists of a catheter with a silicone balloon and a shaft approximately 6 mm in diameter and 15 cm in length. The shaft contains a small inflation channel and a larger central 'treatment' channel for passage of the high-dose-rate source. An injection port is attached to the inflation channel, and a Luer fitting is attached to the treatment channel. An adapter is provided separately that permits connection with any type of after-loading device. A dose of 34 Gy is delivered at a depth of 1–2 cm from the surface of the balloon in 3.4 Gy fractions (twice daily) over 5 days. More than 1500 devices have been implanted worldwide, and the data indicate that placement of the device is safe and easy to achieve after brief surgical training, with excellent cosmetic results [7].

Giovanni Paganelli (European Institute of Oncology, Milano, Italy) presented preliminary data on a new technique termed the IART (intraoperative avidination for radionuclide therapy) procedure. This procedure consists of a first step in which the surgeon intraoperatively injects avidin directly into the tumour bed; this is followed, 1–2 days later, by a second step in which $^{90}Y/^{177}Lu$ radiolabelled biotin is intravenously injected. Avidin will also percolate the tissue of the index quadrant and is drained by locoregional lymph nodes, including the internal mammary chain and upper clavicular. Avidin is not expressed in normal tissues. Because of its positive electric charge and the inflammatory reaction that occurs after surgery, avidin is retained for several days at the site of surgery and provides an 'artificial receptor' that binds intravenous radioactive biotin with a very high affinity (kd 10^{-15}) only at the surgical site.

News on adjuvant and neoadjuvant systemic treatment

This session focused on the importance of tailoring systemic treatments, taking into consideration all possible information on primary cancer as well as patient preferences.

Richard Gelber (Dana Farber Cancer Institute, Boston, MA, USA) indicated that disease and patient characteristics should be evaluated to predict treatment responsiveness. Nolè (European Institute of Oncology, Milano, Italy) indicated that the future direction of chemotherapy should be toward identifying the most tolerable and effective chemotherapy regimens. Looking for new chemotherapy regimens, he highlighted the following objectives: to identify regimens that have fewer subjective toxic effects, including gastrointestinal symptoms and alopecia; to identify regimens that are effective even in heavily pretreated patients, so that significant palliation can be achieved; to identify effective oral drugs; and to combine cytotoxics with endocrine agents and monoclonal antibodies.

Marco Colleoni (European Institute of Oncology, Milano, Italy) addressed the issue of primary endocrine therapy and chemotherapy. He showed that primary endocrine therapy can have high efficacy with a relatively favourable side-effect profile in selected populations. Preoperative endocrine therapy may permit early identification of tumours that are resistant to endocrine therapy that require alternative treatment, and has the potential additional advantage that it can be continued throughout the perioperative period.

Data from the literature indicate that, in patients with an oestrogen receptor-positive tumour, a response rate of 50–70% can be achieved in approximately 3–4 months using traditional endocrine manipulation, for example administration of tamoxifen or new agents such as aromatase inhibitors. Complete pathological remission is achieved in fewer than 10% of the patients. Chemotherapy remains the mainstay of treatment, being considered a more active and better documented option, with objective remission achieved in 70–90% and pathological remission in 15–30% of patients. Higher pathological response rates can be achieved in patients with endocrine unresponsive disease.

Optimal integration of endocrine therapy with chemotherapy in patients with endocrine responsive tumours should be further studied in the laboratory and in clinical trials. In particular, the introduction of aromatase inhibitors and gonadotropin-releasing hormone analogues, administered in combination with chemotherapy, might improve therapeutic results.

In the closing remarks, Carsten Rose (Lund University Hospital, Lund, Sweden) discussed values and limitations of systemic treatments. Recent findings were presented that suggest that the risk for dying from breast cancer in the European Community has fallen by 5% over the period from 1985 to 2000. However, despite increasing use of tamoxifen and chemotherapy in breast cancer, absolute improvements in cure rates are minimal, and at present the new pharmacological therapies can only account for a small proportion of these cures.

Examples of new therapies are endocrine therapy with third-generation aromatase inhibitors, cytotoxic therapy with taxanes, and targeted therapies with monoclonal antibodies such as trastuzumab and the novel bisphosphonates. These therapies are more efficacious than older forms of therapy. However, the estimated clinical value of many of these new therapies is based on data from small randomized studies, with questionable designs and control treatments, and inadequate estimations of long-term safety and toxicity. In addition, the cost of these new anticancer drugs is several times greater than that of older drugs.

Conclusion

New insights into prevention and discovery of markers of therapy outcome and, in broad terms, development of more sophisticated education tools and improvements in communication skills both for patients and professionals must be applied if further progress in our fight against cancer is to be realized.

Competing interests

The author(s) declare that they have no competing interests.

Acknowledgments

The authors gratefully thank Mr William Russell-Edu for his assistance in reviewing the English.

References

1. Schwartz GF, Giuliano AE. Veronesi U: **Proceedings of the consensus conference on the role of sentinel lymph node biopsy in carcinoma of the breast. April 19–22, 2002, Philadelphia, Pennsylvania.** *Cancer* 2002, **94:**2542-2551.
2. Tousimis E, Van Zee KJ, Fey JV, Hoque LW, Tan LK, Cody HS 3rd, Borgen PI, Montgomery LL: **The accuracy of sentinel lymph node biopsy in multicentric and multifocal invasive breast cancer.** *J Am Coll Surg* 2003, **197:**529-535.
3. Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V, Intra M, Veronesi P, Robertson C, Maisonneuve P, *et al.*: **A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer.** *N Engl J Med* 2003, **349:** 546-553.
4. Wallner P, Arthur D, Bartelink H, Connolly J, Edmundson G, Giuliano A, Goldstein N, Hevezi J, Julian T, Kuske R, *et al.*: **Workshop on partial breast irradiation: state of the art and the science, Bethesda, MD, December 8–10, 2002.** *J Natl Cancer Inst* 2004, **96:**175-184.
5. Veronesi U, Orecchia R, Luini A, Gatti G, Intra M, Zurrida S, Ivaldi G, Tosi G, Ciocca M, Tosoni A, De Lucia F: **A preliminary report of intraoperative radiotherapy (IORT) in limited-stage breast cancer that are conservatively treated.** *Eur J Cancer* 2001, **37:** 2178-2183.
6. Edmundson GK, Vicini FA, Chen PY, Mitchell C, Martinez AA: **Dosimetric characteristics of the Mammosite RTS, a new breast brachytherapy applicator.** *Int J Radiation Oncology Biol Phys* 2002, **52:**1132-1139.
7. Gennari R, Perego E, Ballardini B, dos Santos G, Costa A: **Surgical technique of Mammosite RTS implant for accelerated radiation delivery in breast conserving surgery.** *J Exp Clin Cancer Res* 2004, **23:**207-211.