

Adjuvant strategies in breast cancer: new perspectives, questions and reflections at the end of 2007 St Gallen International Expert Consensus Conference

S. Cinieri^{1,2*}, L. Orlando³, P. Fedele¹, A. Cusmai¹, M. D'Amico¹, P. Rizzo¹ & M. C. Chetri¹

¹Medical Oncology Division, Brindisi; ²Emat oncology Division, European Institute of Oncology, Milano; ³Unit of Research Medical Senology, European Institute of Oncology, Milano, Italy

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. The adjuvant strategy of treatment is a 'hot' issue in this 'scenario'. Every 2 years at St Gallen, a nice and cold town in the north of Switzerland, more of 4000 breast cancer experts arrive from every part of the world, to improve their knowledge in this issue. The Consensus Conference with the discussion of 40 international panelists is the zenith of the conference. This report provides a brief presentation and reflections, immediately at the end of the conference, with the objective being to stimulate ideas regarding what should be done tomorrow.

Key words: adjuvant treatment, breast cancer, St Gallen Consensus Conference

introduction

The aims of the 2007 Conference are as follows: 'Update information for improved treatment choices, improve understanding of results from trials: typically aimed at testing therapies, not focused on efficacy or benefit for the individual patient who receives a therapeutic program. Improve selection of predictive factors or predictive tools; revise risk categories for a better estimation of prognosis (relapse and death) and update specifics (subpopulations).'

At the end of St Gallen Consensus Conferences, the panel will publish recommendations, not guidelines, but the relevance in the choices in term of adjuvant treatments of breast cancer patients of these recommendations, through the years after the conference, is enormous.

As in past editions, in St Gallen 2007, it will not result in a list of recipes, but will provide the audience with sets of opinions and discussions on the treatment of patients outside the context of clinical trials.

treatment of breast cancer

The role of adjuvant treatment in breast cancer after the 2005 St Gallen Consensus Conference, was defined in a chart showed in Table 1.

endocrine responsiveness

The first consideration is that breast cancer is a heterogeneous group of diseases.

The previous St Gallen Consensus Panel recognized the primary importance of selecting the therapeutic target first by considering endocrine-responsive, endocrine-non-responsive, and endocrine response uncertain cohorts.

The panel stresses the inadequacies of routine pathology, the use of trastuzumab made HER2 testing a preoccupation, to good end, with endorsements for high-quality testing.

If we continue to build treatment paradigms on biological markers [estrogen receptor (ER) levels, Lymphovascular invasion (LVI), grade, etc.], then we need to focus far more on high-quality pathology. Unfortunately, there is the strong suspicion that most pathology is not that good—and in particular, not good enough for subtle judgments such as whether the tumor is endocrine responsive. A broader agenda of improving pathology including HER2 and ER testing, as well as role of emerging molecular assays, is needed.

endocrine therapies in breast cancer: postmenopausal women

Antagonizing estrogens has become a mainstay of preventing the initiation and progression of breast cancer. Three distinct methods of achieving this are currently available: selective estrogen receptor modulators, ER down-regulators and

*Correspondence to: Dr S. Cinieri, Medical Oncology Division, ASL BR, Brindisi, Italy. Tel: +39-0831-537218; Fax: +39-0831-537918; E-mail: saverio.cinieri@auslbr1.it

Table 1. Chart for treatment choice 2005

Lower risk	ET	ET	NA ⁴ nil
Average risk	ET alone, or CT → ET (CT + ET)	CT → ET (CT + ET)	CT
Higher risk	CT → ET (CT + ET)	CT → ET (CT + ET)	CT

CT, adjuvant chemotherapy; ET, endocrine therapy

inhibition of estrogens synthesis with oral aromatase inhibitors (AIs).

Emerging data from early-stage trials have outlined the value of adding an AI to adjuvant therapy. Studies are underway to determine the optimal duration, the optimal schedule, the optimal AI, whether AIs should be combined with other endocrine agents and whether there are ways to identify optimal candidates for AI therapy.

The most important questions analyzed from the panelists are the following: Is tamoxifen still an option for endocrine-responsive breast cancer (in the absence of contraindications for AIs) and should it be restricted to some specific population?

What is the role of AI upfront, the role of AI switch and how long should the global duration of endocrine therapy be? There is a need of attention in early postmenopausal women to ovarian suppression when we use AIs. Postmenopausal women (especially on the course of AIs) needed as supportive care Ca²⁺ vitamin D3, bisphosphonates, physical exercise and others.

endocrine therapies in breast cancer: premenopausal women

Women under 35 years have a worse prognosis, following surgical treatment of primary breast cancer. Each year younger than 45 years adds a relative 5% to the risk of death from breast cancer. About the endocrine treatments, the panelists responded to the sequent relevant questions. Is tamoxifen alone an option for premenopausal women with endocrine-responsive breast cancer? Is ovarian suppression plus tamoxifen a standard option based upon evidence from advanced disease and from indirect comparisons? Is ovarian function suppression an option in premenopausal women alone or is it an option only for patients who might plan a future pregnancy? What is the type of ovarian function suppression appropriate for these patients (luteinizing hormone-releasing hormone (LHRH) analog, surgical ovarian ablation or ovarian irradiation)? Assuming that the duration of ovarian function suppression with tamoxifene is undefined, what are the recommendations of the panel about this issue? If chemotherapy plus ovarian function suppression are indicated, should their administration be concurrent or sequential? And for patients who plan a pregnancy is there a different choice? Is use of AIs plus ovarian-function suppression (OFS) appropriate for premenopausal women? Should supportive care (against menopausal symptoms and bone loss, physical exercise or others) be prescribed routinely to patients receiving endocrine treatment?

chemotherapies: endocrine-non-responsive diseases

The so-called 'triple-negative' breast cancer disease and the endocrine-non-responsive diseases are still controversial issues in the adjuvant strategy. In these patients, the treatment is very controversial and the choices about the types and the duration of chemotherapy constituted a challenge for the future.

The following are the most important questions, discussed by the experts about this item. In general, should the choice of therapy be different between HER2⁺ (assuming plus trastuzumab) and HER2⁻ (triple negative)? Is the same treatment indicated? For example, anthracycline if HER2⁺? Is it necessary to avoid anthracycline if HER2⁺? Are platinum or alkylating agents indicated if triple negative? For the panelists who think chemotherapy strategy choice is the same (in term of type and/or duration) for HER2⁺ and triple-negative disease: should chemotherapy be independent of nodal status? Are anthracycline or taxanes indicated to all? Are schedules of four times of Adriamycin/Ciclophosphamide (AC) or six times of combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil 'viable'? Do all patients need six to eight courses? Should the following be considered (AC → T dose-dense, Fluorouracil/Adriamycin/Ciclophosphamide (FEC)₁₀₀, high-dose chemotherapy with peripheral blood stem cells support, FEC toxicity adapted, FEC₁₀₀ plus taxotere, taxotere and carboplatinum) as standard for endocrine-non-responsive HER2⁺ disease? For all chemotherapy choices, the issues related to support were also analyzed, such as the questions regarding the routine use of hematopoietic growth factors and of 'cardio protectors'.

anti-HER2 therapies in breast cancer patients

Since the 2005 St Gallen Conference, the most important improvement demonstrated in disease-free survival and overall survival was associated with trastuzumab for patients with HER2⁺ disease. This advance was realized, not only because an effective treatment was being evaluated but also because the patients enrolled in the trials had the targeted disease determined by quality-controlled selection before study entry. The effectiveness of the targeted adjuvant treatment, trastuzumab, was so impressive that the trials reached their objectives earlier than anticipated, thus attenuating the opportunity to assess longer term effects and limiting the number of events available for subgroup analyses. Current evidence is insufficient to identify a cohort of patients with HER2⁺ disease who would not achieve a reduction in the risk of

Table 2. Chart for treatment choice 2005

Low risk	ET	ET	Nil
Average risk HER2 ⁺	ET alone, or CT → ET (CT + ET), trastuzumab	CT → ET (CT + ET), trastuzumab	CT, trastuzumab
Higher risk HER2 ⁺	CT → ET (CT + ET), trastuzumab	CT → ET (CT + ET), trastuzumab	CT, trastuzumab

CT, adjuvant chemotherapy; ET, endocrine therapy

recurrence. At the end of 2006 was published an update of St Gallen 2005 Conference with the title 'First-select the target: better choice of adjuvant treatments for breast cancer patients' (Table 2).

The first 'dilemma' discussed by the panelists is to define the population to treat with trastuzumab.

The panel analyzed some questionable criteria such as size <1 cm, positivity on immunohistochemistry (IHC) expressed with +++ or positivity with other IHC methods and the use of amplification method only.

The relevance of chromosome 17 polysomy, the decision-making process in breast cancer patients with some IHC methods, size <1 cm, N- and endocrine responsive.

Regarding chemotherapy regimen in these patients, the questions and considerations are related to the use of anthracyclines or not for all patients, the use of taxanes, the sequential use of trastuzumab as HERceptin Adjuvant (HERA) model or concurrent with chemotherapies, the use of carboplatinum/docetaxel-containing regimens concurrent with trastuzumab.

preoperative systemic therapies

The use of tumor characteristics which predict the magnitude of response to a given treatment allows a more effective use of primary therapies, identifying patients likely to obtain significant advantage from treatment. Currently, in the preoperative setting expression of ER and progesterone receptor in the tumor are typically associated with increased response to endocrine therapies, while their absence predicts higher response to chemotherapy. Other biological predictive factors include HER2 overexpression. The activity of agents directed against HER1 and both HER1 and 2 overexpressing breast cancer in combination with chemotherapy and endocrine therapy deserves further investigation in the preoperative setting. Chemotherapy remains the mainstay of treatment being considered to be an active and documented option, with objective remission achieved in 70–90% and

pathologic remission in 15–30% of the patients. Integration of endocrine therapy with chemotherapy and targeted agents should be further studied in the laboratory and in clinical trials.

The questions proposed to the panelists regarded the identification of patients candidate to preoperative chemotherapy: tumors <T3 to allow checking of response; endocrine-non-responsive (any size) disease; the inclusion, always, in the schedule of taxanes; and the inclusion of trastuzumab when the disease is HER2⁺.

identification of patients requiring chemotherapy—new considerations

In the next years the use of computers will integrate all the information gathered so far about breast cancer to build robust models for understanding the etiopathogenesis, treatment and prognosis of breast cancer. The identification of molecular signatures to select patients who could be spared chemotherapy and the identification of molecular features which indicate the optimal chemotherapy regimen, in all patients and/or in endocrine response uncertain disease. For these reasons the panelists were invited to discuss and vote about the use of 'Oncotype DX', Adjuvant! Online, MammaPrint®, high and poor-risk patients and the integration of this methods in the daily clinical activity.

conclusions

At the end of the 2007 St Gallen Consensus Conference, after 4 h of intense debate, the majority of questions are clear, but the other questions are confusing, the way to a deeper knowledge of tumor biology and clinical presentation not so close.

All the patients and physicians attend the publications of recommendations, the results of ongoing studies and the 2009 St Gallen international expert consensus on the primary therapy of early breast cancer.