



# Adjuvant therapy of primary breast cancer: Consensus Conference, St. Gallen

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*The International Consensus Conference in St. Gallen, Switzerland, on adjuvant therapy of primary breast cancer was one of the most important scientific meetings in the field. The consensus recommendations are supposed to be implemented worldwide, and influence the outcome of the disease in the majority of patients outside clinical trials. It is believed, as pointed out by Sir Richard Peto (U.K.), that the decrease of the breast cancer mortality rate, which fell in 2000 to the lowest level ever noted before, was due to the cumulative effect of small improvements, including the benefit from all adjuvant treatments. The Conference pointed out several important directions for further development: better collaboration between clinical oncology and basic science; greater support to the multicenter controlled randomized studies; the increasing use of media, especially the Internet. However, the main progress of the Consensus Conference in 2001 is the statement that steroid receptors are of fundamental importance, both as prognostic and predictive biological markers in breast cancer. The recognition of the importance of steroid receptor expression, and the relative importance of cut-off values, resulted in a slight increase in using the endocrine adjuvant therapy. The most crucial question should be whether the effect of adjuvant endocrine therapy with tamoxifen could be even more improved. The answers are expected from several ongoing studies. In addition, the importance of the re-evaluation of known, as well as new prognosticators was emphasized. Therefore, as one of the panelists concluded, the growing body of our knowledge on the early breast cancer adjuvant treatment gave more questions, than answers.*

**KEY WORDS:** Breast Neoplasms; Neoadjuvant Therapy; Prognosis; Consensus Development Conferences

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## INTRODUCTION

**T**he International Consensus Conference in St. Gallen, Switzerland, on adjuvant therapy of primary breast cancer was one of the most important scientific meetings in the field, besides the NIH Consensus Development Conference (1). It brought together about 3,000 people. The abstracts were published in the Supplement 1 of the journal *The Breast*. The Consensus Statements are expected to be published soon in the *Journal of Clinical Oncology*, while the oral reports will appear in Hans Huber's monograph.

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In general, it can be assumed that the Conference made further progress in three different directions. The first was the tendency toward better collaboration between clinical oncology and basic science, through the translational research. Until recently, the translational studies used almost exclusively the paraffin embedded material. Now it is recognized that the banking of tissue and other materials should be projected at the time of designing study protocols. It should allow the targeted research of new biological markers, concomitantly with study progression. The second direction of development was the increasing support to the well-designed multicenter randomized studies, in accordance to the principles of "evidence-based medicine". This could allow, not only shortening the accrual time and getting the answers as soon as possible, but also influencing the quality of clinical research. The third novel direction adopted by the Conference was the recognition of the role of media, especially the Internet. Michael Baum (U.K.) emphasized the increasing responsibility of clinical

investigators and researchers in the field, to inform the public, and especially the patients, about the new developments in basic science, and about the importance of clinical investigations, as the only way towards the progress in adjuvant therapy. If these 3,000 participants give the best possible treatment to their patients, then it is the responsibility on their patients too, to accept the randomization into clinical studies, and thus help the other hundreds or thousands of patients in the future to be better treated, or even cured, said Dr. Baum.

## PROGNOSTIC FACTORS

There were no changes in the list of prognostic factors for node-negative (NO) patients, compared to the Consensus from 1998 (2). Tumor size and grade, steroid receptor (SR) status and age ( $<35 \geq$ ) are still recommended in sub-grouping the NO patients into risk categories. The definition of the group of patients who should not be recommended the routine adjuvant treatment is changed. This is the group with NO disease, whose risk of relapse after 10 years is less than 10%. The former definition concerned the risk of death after 10 years. This means that the slightly larger proportion of patients should be treated by adjuvant therapies. In N+ disease, the Panel again suggested the division according to the level of risk, based mostly on the number of involved nodes.

## PREDICTIVE FACTORS

The main progress of the Consensus Conference in 2001 is the statement that steroid receptors are of fundamental importance, both as prognostic and predictive biological markers. More than two decades clinicians and researchers tried to define optimal method for ER determination and the cut-off value of ER (3). The addition of PR arose new questions, due to the combination of two receptor's status. It was accepted that the term "receptor positivity" means that one and/or the other receptor status was positive (2). In the meantime, it was suggested that the small benefit of tamoxifen in ER-negative patients came from the subgroup with negative, but present low content of ER (4). Therefore, the recommendation of endocrine therapy only to strictly receptor-positive patients could cause that certain patients' population would be deprived of the potential benefit from tamoxifen. This is the reason why the Consensus 2001 changed the recommendation, and suggested the addition of endocrine treatment also to the receptor negative patients with low receptor content.

SRs are still considered the only predictive biological markers for the use outside the clinical trials. All the others, like HER-2, proteases, vascular invasion, genetic markers, are supported by strong, but insufficiently consistent evidence, and therefore

should be further investigated. It is also pointed out that there is no need for new predictive markers, but that it is rather important to re-evaluate the value of the known ones and to improve their use, to avoid both the over-treatment and the under-treatment.

One of the most promising new prognosticators, HER-2/neu, was the subject of notably larger number of oral and poster presentations. Several very intriguing issues are: its prognostic role, as well as the (negative) predicting role for the response to tamoxifen and probably to CMF chemotherapy, and the (positive) predictive significance for the response to anthracyclines and taxanes. In particular, the importance of the level of its positivity for the response to trastuzumab is under study. In addition, the circulating c-erbB-2 protein is the matter of some investigations. Although a very large amount of evidence has been accumulated, there are still some controversial findings, probably due to the unsatisfactory standardized methods for its detection in the past. Although the standardization is now much improved, it is obvious that we have to wait for years to the results of prospective prognostic and predictive studies. In the meantime, an interesting question was pointed out: should we use the HER-2 as prognosticator, or in the selection of chemotherapy regimen? The answer, given by Dr. Martine Piccart (Belgium) was that HER-2 might be used by experienced clinicians, in a particular patient or patients' group, for example, for a choice of the somewhat more intense anthracycline regimens. However, it is still recommended to be preferably used as an investigational marker.

## ADJUVANT CHEMOTHERAPY

The issue of the best chemotherapy regimen is in fact the choice between CMF and anthracycline regimens, said Dr. Piccart. It is broadly accepted that anthracycline regimens add a small, but significant benefit compared to CMF chemotherapy (5). Therefore, anthracycline regimens are the best choice, and CMF can be used in case of cardiac contraindications, or in low risk subgroups. Concerning the best anthracycline regimen, the concern was expressed that ACx4 was a sub-optimal adjuvant treatment, at least for high-risk patients. Based on several studies, it seems that not only the dose, but also the duration of chemotherapy is important. Therefore, the standard should be FAC/FEC/CAF regimen (6). Russel Bassar (Australia) stated that standard doses were superior to less-than-standard doses, however the dose-intensity above the standard failed to show the benefit in adjuvant settings. It is noteworthy to say that the standard doses are those that we have called "high" until recently (7). Enough is enough, but not too much, said R. Bassar.

Concerning the adjuvant use of taxanes, there is no convincing evidence on the optimal doses, sequence and combination with anthracyclines, role of steroid hormone-receptor status and the

definition of subgroups that would benefit most. The more mature results from NSABP B28 study, comparing AC with AC followed by paclitaxel, are awaited: and again, the question of expected superiority of added paclitaxel should be re-analyzed in light of longer duration of treatment. It was concluded that this remains a promising area of research (8).

## ENDOCRINE TREATMENT

As was stated by Sir Richard Peto, there existed a significant benefit from tamoxifen in all steroid receptor-positive women, pre- and postmenopausal, younger and older than 50, lymph node-negative and positive, and irrespective of whether or not they were treated with chemotherapy. A small benefit also existed in SR-negative patients, coming probably from those sub-groups with the low content of SRs. The question for the ongoing and future studies is: whether the effect of adjuvant endocrine therapy could be even more improved. The answers are expected from several ongoing studies. The tamoxifen use for additional five years is addressed by ATLAS (Adjuvant Tamoxifen Longer Against Shorter) study in UK. The rationale for this study is the possibility that the termination of tamoxifen treatment would allow the tumor growth. B. Fisher suggested the opposite situation - that the tamoxifen-dependent growth could compromise the longer use of tamoxifen in an NSABP study (9). The third reason for tamoxifen failure can be the development of tamoxifen-resistance. To overcome the resistance, the use of new generation of aromatase inhibitors has been investigated by several studies (letrozole after five years of tamoxifen in NCIC CTG MA.17/ BIG 01-97 study, exemestane after two to three years of tamoxifen in OEXE 031-C/ BIG 02-97 study, anastrozole after two years of tamoxifen in GABG study IV-C). In addition, potentially greater benefit from aromatase inhibitors than from tamoxifen, suggested in recently published studies of metastatic breast cancer, as well as the combined treatment, are investigated in several other studies (CRC ATAC - Arimidex Tamoxifen Alone and Combination, in UK; IBCSG 18-98/ BIG 01-98 four arm study comparing five years of tamoxifen and five years of letrozole, to the sequence TAM → Letrozole and Letrozole → TAM). The other intriguing question - whether the addition of ovarian suppression to tamoxifen in premenopausal patients can produce a greater benefit than tamoxifen alone - is addressed by some ongoing studies (ABC trial and CRC adjuvant breast trial for patients under the age of 50). Thus, it seems that the treatment of thousands of women with tamoxifen, during the last decades, created more questions, than answers.

On the issue of ovarian ablation and ovarian suppression, there are many open questions too. Although the ovarian ablation is defined for the first time as a definitely approved adjuvant treat-

ment for N+, SR+ premenopausal patients with lower risk, it is stated that the data about the role of steroid receptor status in predicting the response to ovarian ablation are insufficient, since the majority of earlier studies did not determine SRs (10). The other open questions were also stated: the comparison of ovarian ablation to ovarian suppression, the role of treatment-induced amenorrhea, the potential of ovarian ablation in reducing the contralateral breast cancer etc. In particular, two ongoing studies are addressed to the value of ovarian ablation in comparison to chemotherapy (Danish study DBCG 89 B-D+CSB II-2), or with the addition of tamoxifen, in comparison to the same endocrine combination + chemotherapy (IBCSG trial 11-93). There are more ongoing studies, concerning the ovarian suppression with LH-RH analogues. The early results of IBCSG trial 11-93, presented on the Conference, suggested that the addition of four cycles AC or EC to the ovarian ablation/ suppression, in premenopausal N (1-3), SR+ patients - did not produce better outcome at the median follow-up of four years. These results suggested that the suppression of ovarian function could be the essential component of an adjuvant treatment in premenopausal patients classified as having an endocrine responsive breast cancer (11).

## COMBINED CHEMO-ENDOCRINE TREATMENT

Monica Castiglione (Switzerland) addressed the issue of negative interactions between chemo- and endocrine therapy given concomitantly. Although the Oxford's meta-analyses confirmed a small superiority of the chemotherapy added to endocrine therapies in SR+ patients, there existed a certain concern about that, since no study included in the overview did show clear benefit. Anyhow, most of the Panel experts supported the conclusion that there was no clear advantage of combining chemo-endocrine treatment. M. Castiglione said that in receptor-positive patients the chemotherapy seemed to be superfluous, while in receptor-negative patients it was the endocrine treatment that was excessive. Therefore, the combined treatment should be reserved for patients with borderline positivity of steroid receptors. If chemo- and endocrine treatments are combined, then the standard should be chemotherapy + tamoxifen (and not ovarian ablation).

## SURGICAL PROBLEMS

Many open questions concerning the DCIS were stated: the prediction of local recurrence should be further investigated, as well as the optimal adjuvant treatment. Anyhow, there is still no consensus about the best treatment strategy of DCIS, as it was said. Sentinel node biopsy is the other field of intensive investigations, since it provides the possibility of avoiding the axillary dissection.

## RADIOTHERAPY

The data exist that more than 40% of patients with locally advanced breast cancer, having been treated with radiotherapy alone, are still alive after 10 years. Therefore, the question is whether the radiotherapy might be a curative treatment in locally advanced breast cancer, said Dr. John Yarnold (U.K.). Locally advanced breast cancer patients with the involved ipsilateral supraclavicular lymph nodes, actually being classified as stage IV have the outcome more alike to the clinical stage IIIb. Therefore, the initiative has been raised to return to the previous classification of this particular group of locally advanced breast cancer patients.

## CONSENSUS RECOMMENDATIONS

The recommendations for the adjuvant treatment outside clinical trials has slightly been changed, compared to the consensus from 1998. Shortly, concerning the N-negative disease with intermediate risk, tamoxifen with or without chemotherapy is recommended as an endocrine treatment of choice, and ovarian ablation/suppression is clearly suggested for investigation. Moreover, it was stated that chemotherapy might be avoided in this subgroup. In high-risk postmenopausal N-negative patients, chemotherapy also may be avoided, if they are R+. For R-negative postmenopausal patients, the optimum choice is still chemotherapy, but, nevertheless, tamoxifen may be added, if low receptor content is present. For high-risk premenopausal patients, the anthracycline-based chemotherapy is recommended, followed by tamoxifen, if R+.

Concerning the node-positive disease, the proposed change is the exclusion of low-risk N+ patients (according to the number of involved lymph nodes), from those who should be necessarily treated with adjuvant chemotherapy. As it is well known, in the last Consensus all patients with node-positive disease were recommended the chemotherapy, irrespective to the level of the risk. It was influenced by the previous results of the NSABP B-20 study (12), and the misinterpretation of the Bernard Fisher's statements. He has never said that all N+ patients have to be treated by chemotherapy. He said that all N+ patients could benefit from chemotherapy, and there lies the difference, explained B. Fisher (USA) himself. Anyhow, low-risk N+ patients are now again in the focus and the new recommendation retains the possibility of giving them the endocrine treatment alone, if they are receptor positive. Interestingly, our National Protocol for the Breast Cancer Treatment (13) retained the recommendation of endocrine treatments alone for SR positive patients with 1-3 involved lymph nodes.

The new approach that is suggested is the recommendation of tamoxifen addition to chemotherapy in all N+ patients with negative, but present steroid receptors.

## CONCLUSION

In conclusion, it is evident that the number of patients who should be treated with chemotherapy is slightly decreased, while the number of patients who should be treated with endocrine therapy is slightly increased. This is in accordance with the main conference conclusions about the fundamental role of steroid receptors.

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