Satellite Symposium I

International Consensus Meeting on the Treatment of Primary Breast Cancer 2001, St. Gallen, Switzerland

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The St. Gallen Consensus Meeting was held in conjuction with the 7th International Adjuvant Therapy of Primary Breast Cancer Conference in St. Gallen, February 21-24, 2001. About 2,800 delegates from 68 countries joined the meeting. All panel members were internationally well known breast cancer experts and leading members of national and/or international cooperative breast cancer study groups. The panel summarized the relevant findings in breast cancer research since the previous Consensus Meeting in 1998. The most important topics were the increased role of endocrine therapy, the loss of enthusiasm for high-dose therapy, new agents, the approach to the axilla, postoperative radiotherapy and incorporation of patients' preference. In making these guidelines and recommendations the panelists considered the extrapolation of results of randomized clinical trials, the patients' risk of relapse, the prediction of treatment effects and patients' preference. They did not consider the availability of national resources and the design of educational strategies, neither for patients nor for the public[1-3].

Risk Factors

The risk factors remained similar to those of 1998: the number of involved nodes and in absence of node-positivity pathological tumor size, grade, ER and PgR expression and age. However, no group was defined who should not be treated although no treatment in patients with very favourable prognostic factors might be a reasonable decision to manage the patients' disease. Other risk factors were considered but not found suitable for general use presently, mainly because of lack of standardization of current techniques. The category of "elderly" patients was abolished. The cut-off for the age definition was felt to be arbitrary and not useful. This change was primarily made due to the recognition of the lack of knowledge concerning trade-offs between treatment burdens, risk of relapse, morbidity, mortality and age within the previously defined elderly category.

Endocrine Responsiveness

The primary treatment selection is based on the endocrine responsiveness of the disease. The threshold for ER and PgR positivity was lowered to 1% positive cells on immunohistochemical analysis. There was also a trend for adding patients with tumors up to 2 cm and high differentiation (grade 1) to the minimal risk category. In case these patients meet also all other favourable prognostic tumor and patient characteristics a no-treatment option could be considered as mentioned above.

Assignment of Adjuvant Systemic Therapy

Up to 1998 the assignment of adjuvant systemic therapy was made based on 3 risk categories (low risk, intermediate risk and high risk). In 2001 the patient categories of intermediate risk and high risk were merged. Thus, the assignment of adjuvant systemic therapy is now determined only by two risk categories, low risk and high risk.

The primary determination of systemic therapy is made by categorizing the patients' malignancy in endocrine responsive disease versus endocrine non-responsive disease. Of course, menopausal status, age and patients' preference remain important factors within both categories. The assignment of

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Abbreviations:
ER, Estrogen receptor; PgR, Progesterone receptor

Table 1. New Definition of Risk Categories for Patients with Node-Negative Breast Cancer

Risk Category	Endocrine Responsive[1]	Endocrine Non-Responsive[1]
Minimal/Low Risk[2]	ER and/or PgR positive, AND all of the following features: pT* ≦ 2 cm, AND Grade 1**, AND Age*** ≧ 35 years	Not Applicable
Average/High Risk	ER and/or PgR positive, AND at least one of the following features: pT* > 2 cm, OR Grade 2-3**, OR Age*** < 35 years	ER and PgR negative

[1]Responsiveness to endocrine therapies is related to expression of estrogen and progesterone receptors in the tumor cells. The exact threshold of estrogen and / or progesterone receptor staining (with currently available immunohistochemical methods), which should be used to distinguish between endocrine responsive and endocrine non-responsive tumor is unknown. Even a low number of cells stained positive (as low as 1% of tumor cells) identify a cohort of tumors having some responsiveness to endocrine therapies. Probably, as typical for biological systems, a precise threshold does not exist. However empirically chosen, about 10% positive staining of cells for either receptor might be considered as a reasonable threshold, accepted by most. Furthermore, it is clear that the lack of staining for both receptors confers endocrine non-responsiveness status.

[2]Some Panel members recognize lymphatic and/or vascular invasion as a factor indicating greater risk than minimal or low. On the other hand, mucinous histological type is associated with low risk of relapse.

*pT = pathological tumor size (i.e., size of the invasive component).

**Histologic and/or nuclear grade.

***Patients with breast cancer at young age have been shown to be at high risk of relapse.

treatment to an individual patient includes but is not limited to the integration of risk and responsiveness of the disease to the assigned adjuvant therapy.

Surgery

It is now accepted that reconstruction after mastectomy is a safe procedure in the management of the primary tumor. Regarding the approach to the axilla and sentinel node biopsy the following statement was created by the panelists: A negative sentinel node biopsy in experienced hands and with proper pathologic work-up can avoid a full axillary dissection with a higher than 90% sensitivity and specificity. However, there was no consensus on the routine use of sentinel node biopsy and on the surgical experience required to introduce this procedure as routine in daily practice. There was also no consensus on the use of immunohistochemistry for pathologic work-up of the sentinel node. Again, there was no consensus on the significance of micrometastases.

Radiation Therapy

Local treatment matters. Radiotherapy after breast-conserving surgery is clearly indicated. Radiotherapy after mastectomy should be considered for patients at high risk for locoregional recurrence. Obviously it should not be used to replace optimal surgery. There is a lack of long-term safety data when used together with adjuvant anthracyclines and taxanes. Radiotherapy should be started within 6 months of definite surgery. It is usually given after completion of adjuvant chemotherapy.

Node Negative Disease

Patients at low risk should receive tamoxifen for 5 years. In premenopausal patients goserelin given for at least 2 years showed very encouraging results. Patients with node negative disease but at high risk should receive similar therapy as node positive patients. Patients with ER and PgR negative disease should receive four to six cycles of adequate chemotherapy. In ER and/or PgR positive disease endocrine or chemo-endocrine therapy can be given. When CMF therapy is given, it should be classic CMF with oral cyclophosphamide for 14 days every 28 days. In high risk patients antracyclines can be considered.

Node Positive Disease

Anthracycline containing chemotherapy (CEF, CAF and similar regimens) has been shown to be superior to CMF. High dose chemotherapy should only be given in randomized clinical trials. The role of taxanes is presently regarded as investigational. In ER and/or PgR positive disease chemotherapy and tamoxifen is superior to chemotherapy alone. Tamoxifen alone may be justified in postmenopausal patients.

Specific Treatments

1) Ovarian Ablation/Ovarian Function Suppression

It has been clearly shown that ovarian ablation or ovarian function suppression is effective. However, the overall morbidity is unknown.This is of even

greater concern in very young patients and for ovarian ablation. Based on the overall evidence available today, ovarian function suppression and tamoxifen can be regarded as a proper treatment in premenopausal patients with clearly hormone-dependent disease. The role for temporary ovarian suppression has been strengthened. In particular goserelin has been clearly shown to be at least as effective as chemotherapy in seven clinical trials. Furthermore, the long term toxicity also seems to be reduced. However, the optimal duration of ovarian function suppression in these patients is unknown. In the seven trials considered during the meeting goserelin was given for two to five years.

2) Tamoxifen

The standard duration of adjuvant tamoxifen is five years. A beneficial effect after completion of the five year tamoxifen treatment can be observed. The use of other selective estrogen-receptors (SERMs) is not justified at present. The use of tamoxifen in association with aromatase inhibitors is currently being tested. In premenopausal patients the combination of tamoxifen with ovarian function suppression should also be studied in the near future.

3) Chemotherapy

On average anthracycline-containing therapies are superior to average CMF's. Direct comparison of CMF to CAF or CEF showed the anthracycline-containing regimens to be superior. The optimal use of anthracyclines is still not known, but lower doses of anthracyclines seem to be clearly less effective. On the other hand regimens with higher doses were not more effective. Higher doses of anthracyclines and alkalating agents (usually given with growth factor support) are associated with an increased incidence of leukemia and myelodysplastic syndromes.

Ductal Carcinoma in situ

There was an agreement that too many mastectomies for this condition are performed. Adjuvant radiotherapy reduces the risk of recurrence by about 50%. Tamoxifen reduces the risk of recurrence up to about 50%. However, the absolute gain in low risk disease is very low. No consensus was reached on ER status to guide adjuvant therapy. Sentinel node biopsy can be considered in large high grade lesions.

Summary

The role of sentinel node biopsy has increased over the last three years. Nodal status is no longer a main criterion for assignment of systemic adjuvant therapy. In premenopausal patients with clearly hormone dependent disease, endocrine therapy is standard irrespective of chemotherapy. An increased role, especially for goserelin and anthracyclines in the adjuvant therapy of breast cancer has been established. However, more large scale clinical trials are needed.

Several important questions have to be answered in the near future:

- The role of ovarian function suppression associated with tamoxifen
- The role of aromatase inhibitors
- The usefulness of taxanes and the role of high dose chemotherapy in ER/PgR absent disease should be studied
- The role of trastuzumab with chemotherapy should be clarified

The 9th International Conference on Adjuvant Therapy of Primary Breast Cancer (ABC) and Consensus Meeting is planned for March 13th-15th, 2003.

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Members of the Panel are listed below. All had a significant input to the discussion and the manuscript.

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