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Who should receive adjuvant treatment?

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There are several guidelines and recommendations from various national and international experts that provide information on what should be considered a standard adjuvant systemic treatment for women diagnosed with operable breast cancer. These are available on the web and in various specialty journals. Clinical trials with new adjuvant systemic therapies are being conducted to improve care and expand knowledge in a field, which has been a model for successful efforts, leading to a significant reduction in mortality during past years.

An analysis on the process of tailoring adjuvant therapies for individual patients should take into account the following domains:

- **Estimation of risk of relapse** for a patient with invasive breast cancer as part of a population including individuals with similar characteristics. Obviously, current information on tumor and patient characteristics may be different from that included in studies of the past, and there might be some shifting of allocation to one prognostic group or the other due to evolution of knowledge (e.g., sentinel lymph node and micrometastases). A risk of systemic relapse of about 10% has been considered as high enough to be the basis for a treatment proposal.
- **Estimation of endocrine responsiveness** of the tumor. The choice of treatment is based upon the assumption that micrometastatic disease, target of adjuvant systemic therapies, is similar in terms of responsiveness to the primary tumor. Typically, estrogen and progesterone receptor expression in the primary tumor is associated with increased benefit from adjuvant endocrine therapies. It has been recognized that endocrine therapies are useless and potentially harmful when no steroid hormone receptors are expressed.
- **Extrapolation from results of clinical trials** is a required information helpful in order to adapt available treatment for an individual. Trials were conducted on populations of patients with disease characteristics, which might be only partially relevant for the patient for whom an adjuvant therapy should be proposed. Beneficial average treatment effects might not fit all individuals.
- Degree of belief in the data related to treatment effects and **prejudices** of physicians in favor of one treatment or another, are important features in determining the choice of treatment and even whether to propose therapy or not. The historical context within which trials were conducted and their results applied in a given environment has an important influence upon treatment choice.
- **Patients' preferences**. Research in this field, using trade-off approaches, led to the conclusion that patients indicate adjuvant therapy as worthy even for a relatively small outcome benefit.

It was recognized at the latest edition of the expert panel meeting in St. Gallen (March 2003), that only few patients should not be proposed an adjuvant systemic treatment. The availability of endocrine treatments and their demonstrated beneficial effects on the risk of metastases, as well as on the risk of new breast cancer allowed the broadening of the indication to those patients who are at the minimal category risk of relapse. On the other hand, patients with tumors that do not express any steroid hormone receptors are likely to have an increased risk of relapse, thus eligible for cytotoxics treatments. Higher chance for competing causes of disease and mortality on one hand, and limited malignant potential of the disease on the other, are probably the main conditions for which adjuvant systemic therapy might not be proposed.

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Tailored adjuvant therapies

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Background: The Oxford Overview data show that chemotherapy plus 5 years of tamoxifen is more effective than chemotherapy alone. The addition of 5 years of tamoxifen to adjuvant chemotherapy in women under the age of 50 results in an additional ~ 21% reduction in the odds of recurrence and in the older group, 50-69 years of age, in an additional 19% reduction. However, these results and the data of several clinical trials have shown to be based on the mixture of endocrine-responsive and endocrine-non-responsive-disease and therefore to be confounded and of limited help for patient care.

Material and Methods: We conducted 2 trials in pre and postmenopausal women with node-negative breast cancer investigating the role of combination chemo-endocrine therapy (CMFx6+Goserelin x18 months) compared to chemotherapy alone (CMFx6) and to endocrine therapy alone (Goserelinx24 months) in premenopausal and chemo-endocrine therapy (CMFx3 followed by Tamoxifen up to 5 years) compared to endocrine therapy alone (Tamoxifen for 5 years) in postmenopausal women.

Results: Overall in both trials the combination of chemo- and endocrine therapy showed better results than either modality alone (CMF alone and Goserelin alone in the premenopausal and tamoxifen alone in the postmenopausal setting). Analysis of subgroups predefined by hormone-receptor content in the primary tumor, however, showed that patients with receptor positive disease did not benefit from the addition of chemotherapy to the endocrine treatment.Patients with receptor negative disease showed in both studies a benefit from the combination of chemo-endocrine therapy, in particular in younger age ($\leq$39 years).

Conclusions: In premenopausal women adjuvant treatment has consisted mostly of chemotherapy independently from hormone-responsiveness. Recent data have shown the importance of endocrine manipulations, in particular in the youngest subgroup (<35 years of age). In women under 50 with hormone–responsive breast cancer who receive both adjuvant chemotherapy and 5 years of tamoxifen, it is unclear whether any additional benefit is derived from suppression of ovarian function and whether chemotherapy is needed at all in the presence of optimal endocrine therapy.

Patients > 50 with endocrine non-responsive disease benefit substantially from adjuvant chemotherapy and chemotherapy-related questions should be addressed in this population. The worth of additional chemotherapy to 5 years of tamoxifen should be questioned in women with endocrine-responsive disease. The focus in this patient population should be the development of new endocrine regimens. We think therefore that it is time to move away from treating patients according to risk into treating patients by endocrine responsiveness.

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The prognostic and predictive role of HER-2 and topoisomerase II alpha in breast cancer (BC).

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Although a relevant amount of data indicates that HER-2 positivity is associated with an increased risk of BC relapse, HER-2 is not yet recognized as a standard prognostic factor, mainly because of some heterogeneity in testing procedures used in current laboratory practice. The predictive role of this marker in the adjuvant treatment of BC has been largely investigated. Six retrospective studies have suggested that the largest benefit deriving from the use of an anthracycline (A)-based treatment in the adjuvant setting is observed in the cohort of patients carrying HER-2 + tumors. In the last years it has been reported that HER-2 might not be directly involved in the prediction of response to A and that topoisomerase II alpha (topo IIA) might be the most appropriate predictive marker. This hypothesis is supported by the following findings: a) topo IIA is the molecular target of A; b) topo IIA gene amplification is observed in 20-40% of HER-2 + tumors while it is uncommon in HER-2 negative BC. Some retrospective studies have suggested that the highest level of efficacy of A is observed in the cohort of tumors carrying both HER-2 and topo IIA gene amplification. One of these studies has highlighted that the superiority of an A-based regimen over CMF in the adjuvant treatment of node + BC is confined to the subgroup of patients with HER-2 and topo IIA gene amplified tumors. Although pre-clinical and early clinical studies support the predictive value