Symposia

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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

of topo IIA, we are still far from the use of this marker in current practice because we need proof of principle trials. To this end, two large studies are ongoing. The first of these two studies aims to perform a meta-analysis of four clinical trials which have compared an A-based regimen to CMF in the adjuvant setting. Tumor samples from patients entered in these four trials will be centralised and HER-2 and topo IIA gene status will be evaluated.The second study aims to test prospectively the predictive value of topo IIA in a group of approximately 400 patients with large operable endocrine-resistant BC treated with pre-operative single-agent epirubicin. These two ongoing studies might have an impact on future standard practice.

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New endocrine agents

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Oestrogens are the dominant hormonal stimulant for breast cancer growth. For many years the antioestrogen tamoxifen has been the first line endocrine therapy for patients with early or late stage steroid receptor positive breast cancer, and as such it has resulted in a reduced mortality from the disease. Laboratory data suggest that the partial agonist activity of tamoxifen creates a limit on its efficacy and a possible mechanism for acquired resistance. These concepts supported the development of aromatase inhibitors which block the synthesis of oestrogens in post menopausal women. These agents do not bind to the oestrogen receptor (ER) and therefore possess no oestrogenic activity. Additionally a new type of steroidal antioestrogen (fulvestrant) has been developed that down regulates ER levels and also lacks any agonist activity. Recent clinical data have revealed that 3rd generation aromatase inhibitors are more effective in advanced disease than tamoxifen. Also the aromatase inhibitor, anastrozole has shown greater efficacy than tamoxifen or a combination of the 2 in the adjuvant setting. Ongoing adjuvant trials of aromatase inhibitors involve more than 40,000 patients. Fulvestrant has been found to be similar in efficacy to anatrozole in advanced disease. The immediate challenges are to maximize the benefit from these new agents and to investigate their optimal use in combination with agents that target growth factor pathways that may mediate resistance.

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Lymphangiogenic growth factors and tumor metastasis

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Angiogenesis and permeability of blood vessels are regulated by vascular endothelial growth factor (VEGF) via its two receptors VEGFR-1 and VEGFR-2. The VEGFR-3 receptor does not bind VEGF and its expression becomes restricted mainly to lymphatic endothelia during development. We have found that homozygous VEGFR-3 targeted mice die around midgestation due to failure of cardiovascular development. We have also purified and cloned the VEGFR-3 ligand, VEGF-C. Transgenic mice expressing VEGF-C show evidence of lymphangiogenesis and VEGF-C knockout mice have a lymphatic vascular phenotype. The proteolytically processed form of VEGF-C binds also to VEGFR-2 and is angiogenic. VEGF-D is closely related to VEGF-C, similarly processed and binds to the same receptors. Thus VEGF-C and VEGF-D appear to be both angiogenic and lymphangiogenic growth factors. VEGF-C overexpression led to lymphangiogenesis, intralymphatic tumor growth and lymph node metastasis in several tumor models. Furthermore, soluble VEGFR-3, which blocked embryonic lymphangiogenesis, also blocked lymphatic metastasis in breast and lung cancer models.

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Angiogenesis and tumour pathophysiology

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A solid tumor is an organ comprised of neoplastic cells and host stromal cells nourished by the vasculature made of endothelial cells - all embedded in an extracellular matrix. The interactions among these cells, and between these cells, their surrounding matrix, and their local microenvironment, control the expression of various genes. The products encoded by these genes, in turn, control the pathophysiologic characteristics of the tumor. The tumor pathophysiology governs not only the tumor growth, invasion and metastasis, but also the response to various therapies. In my presentation today I will discuss insights revealed by intravital microscopy (IVM) into the molecular, cellular, anatomical and physiological workings of tumors and how these insights have facilitated the development of improved strategies for cancer detection and treatment. I will focus largely on the work done in my laboratory on the role of host-tumor interactions in the integrative pathophysiology of tumors,and convey the following points: Tumor vessels are abnormal in their organization, structure and function. These abnormalities contribute to heterogeneous vascular permeability, blood flow, and microenvironment. Tumor interstitial matrix is formed by proteins secreted by host and tumor cells as well as those leaked from the nascent blood vessels. Tumor interstitium is heterogeneous with some regions fairly permeable while other regions are difficult to penetrate. Relaxin can permeabilite the tumor matrix. Interstitial hypertension is a hallmark of solid tumors, and results from vessel leakiness, lack of functional lymphatics, and compression of vessels by proliferating cancer cells. Cancer therapy is plagued by two major problems – physiological resistance to drug delivery and oxygen, and genetic and epigenetic mechanisms driven drug resistance. Anti-angiogenic therapy has the potential to overcome these problems. Furthermore, judicious application of this therapy can normalize the tumor vessels and make them more efficient for delivery of oxygen and drugs. Combined anti-angiogenic and conventional therapies appears promising in the clinic. References: R.K. Jain,et al. Nature Review, 2002 R.K. Jain, et al, Science, 2002 R.K. Jain, et al, Nature Medicine, 2003

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Vascular targeting trials

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Tumour vascular targeting therapy exploits differences between normal and tumour blood vessels with the aim of reducing blood flow to the tumour sufficient to cause tumour cell death. Although it is considered different from anti-angiogenic therapy where the main aim is to prevent the development of new tumour vessels, it is becoming increasingly apparent that both types of therapy have overlapping activities. Differences between tumour blood vessels and normal vessels relates, partly to their immaturity which is associated with a different cytoskeleton and lack of pericytes and smooth muscle, partly to their chaotic distribution and, partly to their endothelial surface which may have a different integrins and cadherins. The distinguishing feature of vascular targeting agents in-vivo is that they induce haemorrhagic necrosis of tumours within hours of administration. Unless they have additional anti-tumour activities they are unlikely to induce major tumour responses when given alone, as the tumour cells closest to normal tissue will obtain their blood supply from that tissue. However major tumour regression is seen in vivo when combining vascular targeting agents with cytotoxic chemotherapy, radiotherapy or radiolableed antibodies.

The lack of expected responses with single agent vascular targeting agents has required the development of surrogate endpoints to determine if they are acting on their intended target. Serial dynamic MRI scans are most frequently used to obtain a pharmacodynamic endpoint, as serial PET scanning requires short half life isotopes from an adjacent cyclotron to measure blood flow.

Dynamic scans have confirmed that many of the following drugs act as vascular targeting agents in patients. 5,6-Dimethylxanthenone-4-acetic acid (DMXAA) is thought to act through local TNF induction. Four tubulin binding agents Combretastatin A4P (CA4P), AVE8062A, ZD 6126, and ABT-751 are in the clinic with CA4P having progressed to combination trials. These agents have a very different toxicity profile to cytotoxic chemotherapy. Only when the combination trials are completed will we know whether the therapeutic window is sufficient to induce major tumour regressions with acceptable toxicity.