by high uPA and/or PAI-1 values, improved efficacy of an anthracycline-containing regimen in comparison with CMF can be predicted by *c-erbB-2* determination. This prospective randomised trial will be performed within the framework of the BIOMED-2 programme.

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Thanks to intensified effects of screening and early detection the percentage of patients diagnosed with node-negative breast cancer is ever increasing and well beyond 50%. Nodal status is still the strongest factor indicating prognosis. Negative axillary nodes identify a group of patients known to be at lower risk of recurrence and metastasis with approximately two-thirds being cured. However, one-third of node-negative breast cancer patients will eventually relapse. Improving the fate of these patients at risk requires firstly their

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identification and second the offer of an effective treatment which changes the eventual outcome significantly. Prognostic factors are correlated to the clinical course of disease and allow patients at different risks to be identified. However, to be of clinical use it is not sufficient for these factors to be associated with a biological or clinical endpoint (i.e. relapse or tumour-related death), they must be able to guide a therapeutic decision that results in a more favourable outcome than if the marker results are unknown. These outcomes include higher cure rates, prolonged survival, prolonged disease-free survival, improved quality of life or identical outcomes with lowered cost of care [1]. A parameter is only useful if it places the patient into a subgroup that is highly likely to benefit from the therapy, or into a group that can be spared the toxicity of therapy because the outcome is favourable even without therapy, or because therapy is unlikely to work.

The last two decades provided sufficient evidence that breast cancer should be considered a systemic disease very early in its development. Consequently, systemic treatment has been applied to patients known to be at increased risk for cancer relapse after local treatment. Thus, adjuvant systemic chemotherapeutic and/or hormonal therapy has been applied firstly to node-positive patients. Since this approach has been highly successful in increasing relapse-free and overall survival, systemic adjuvant treatment has been extended to include node-negative patients [2,3]. At present, there is ample evidence that any group of breast cancer patients benefits from systemic chemo- and/or endocrine therapy. Following adjuvant poly-chemotherapy and/or hormonal treatment the proportional reductions in risk for recurrence and cancer-related death are similar in high- and low-risk patients. According to a recently published meta-analysis of randomised trials, adjuvant poly-chemotherapy produces an absolute improvement of approximately 7% (node-negative patients) and 11% (node-positive patients) in 10-year survival for women aged under 50 years at presentation with early breast cancer, and approximately 2% (node-negative) and 3% (node-positive) for those aged 50–69 years [4]. A meta-analysis of randomised studies using tamoxifen also demonstrated proportional reductions in risk for recurrence and cancer-related death similar for women with node-negative and node-positive disease. According to the different risks the absolute recurrence and mortality reductions were greater in node-positive women. In the trials of approximately 5 years of adjuvant tamoxifen the absolute improvements in 10-year survival were 10.9% for node-positive and 5.6% for node-negative women. These benefits appeared to be largely irrespective of age, menopausal status, and whether chemotherapy had been given to both groups. Similar results were achieved with ovariectomy [5]. However, adjuvant therapy is only worthwhile if the improvement in outlook is great enough to more than balance the cost and toxicity of therapy. The absolute number of patients who benefit compared with the total number of patients treated in any given group depends on the risk profile: the lower the risk, the lower is the absolute percentage of patients who benefit. In absolute terms patients with low-risk tumours gain much less absolute benefit than patients with high-risk tumours. Nevertheless, even a modest improvement of survival in individual patients is generally accepted as worthwhile to apply adjuvant therapy. In a recent survey amongst American breast cancer patients the median acceptable extension of life expectancy as a benefit from adjuvant chemotherapy was 3–6 months, and acceptable reduction in recurrence risk was a mere 1.0% [6].

Knowing that adjuvant systemic treatment has the potential to improve outcome in almost all breast cancer patients, these days the question "whether a patient is at a risk high enough to justify the burden of toxicity" has shifted to the question "whether the risk of an individual patient is low enough to justify abstaining from adjuvant treatment". Therefore, decision making on adjuvant therapy currently raises the following demands: (1) to identify patients at very low risk in order to spare these individuals from systemic therapy whose potential benefit is not worth the costs and toxicity of adjuvant treatment; and (2) to identify the most efficacious systemic treatment modality or combinations thereof that combine the highest promise for success with the lowest side-effects for the individual patient. This especially encompasses the characterisation of those tumours which are resistant to a given treatment modality or drug and, alternatively, those which are very likely to respond.

Accordingly at the 1998 St Gallen Meeting on the adjuvant treatment of breast cancer systemic therapy has been suggested for most patients withholding such treatment only in patients at very low risk. Besides nodal status there are several established indicators available which for years have been proven useful and reliable to predict prognosis: tumour size, receptor status, tumour grade and patient's age [7]. Combining these parameters, it is possible to characterise the node-negative patient group which is at a very low risk: (<1 cm tumour size, receptor-positive, grade 1, age >35 years) [8,9]. Although the level of risk that is considered 'very low' and allows refraining from systemic treatment is not clearly defined, the risk of recurrence of this patient group is below 10% and their chance to benefit from any form of systemic therapy does not exceed 1–3%. This group encompasses at most 5% of all node-negative patients. In all other patients benefit from adjuvant treatment is currently considered sufficient to render adjuvant chemo-hormonal therapy mandatory outside of clinical trials.

The target of additional prognostic factors would be (1) to identify a subgroup of patients at higher risk

amongst this group of 'very low risk' tumours; or (2) to identify a subgroup of 'very low risk' amongst those node-negative patients who are currently considered to be at medium or high risk.

The last decade observed a vast increase in the number of parameters which claim to add prognostic information in certain subsets of breast cancer patients. However, of the numerous morphological and biological parameters which have been suggested as prognostically significant in breast cancer, hardly any held true for node-negative patients. Detection of micrometastatic breast cancer cells in bone marrow [10], UPA/PAI1 (urokinase plasminogen activator/plasminogen activator inhibitor 1) [11], cathepsin D [12] and Her-2/neu (although only in small tumours <2 cm) [13,14] are amongst the latter. To make things worse, there is no common understanding on how to test these factors to achieve the most reliable information. The results on their prognostic relevance differ considerably in the numerous studies published, at least in part due to different methods for detection and considerable interlaboratory variance [15,16]. Currently, there is no evidence that using these new factors, in addition to the established parameters mentioned above, would considerably change the proportion of patients who are considered to be at very low risk: according to calculations made by Ravdin [17] a substantial change in calculated risk for an individual patient would occur only if the parameter in question confers a high independent relative risk and has a high or low prevalence of positive results. Furthermore, assuming a proportional improvement in survival from systemic therapy of approximately 30% (which is reported in the recent meta-analyses [4,5]) at most 3% of patients in the 'very low risk group' ($<10\%$ mortality rate in the absence of systemic treatment) will profit from systemic therapy. No matter how powerful the prognostic factor used, there is no subgroup into which patients would fall in which the absolute benefit exceeds 3% [1]. This sets the stakes very high for a new parameter to be of sound clinical relevance in a low-risk population. Thus, the prognostic factors available for node-negative breast cancer are sufficient for clinical use, there is no clinical need and hardly any chance for better prognostic factors.

However, there is still a need to improve quality control on the established parameters: there is consensus that axillary node staging requires histological examination of no less than 10 nodes. This demand is still not met in every case. Furthermore thorough evaluation of axillary nodes in patients staged as pN0 reveals metastatic tumour in more than 10% of cases [18]. Immunohistochemical staining for cytokeratin in 'tumour-free' axillary nodes further detects micrometastases in some cases [2]. Although currently there is no evidence that this false staging changes the fate of these patients (they are usually considered high risk node-negative and receive adjuvant treatment), it demonstrates the need to improve further the assessment of nodal status. With respect to tumour size, there is no agreement whether size needs to be measured before or after formalin fixation (which usually causes shrinking of tissue). For assessment of receptor status three methods are currently in use: immunohistochemistry, enzyme immunoassays or ligand binding assays. The immunological methods use various different commercially available antibodies, and immunohistochemistry is either performed on fresh-frozen or formalin-fixed tissues. Results vary depending on the method used, the antibodies utilised and whether fresh or fixed tissue is used. It is unclear to date, what method is the most reliable and should be prefered. With breast conserving surgery there is agreement that the tumour has to be removed 'in sano'. However, a final definition of 'clear margins' or the required thickness of clear margins are still missing [19]. To conclude, there are many ways in which assessment and reliability of established, clinically useful prognostic parameters could be improved. Starting this task is a matter of urgency.

For these reasons, it is difficult to justify a significant amount of research money and research effort being expended in an unpredictable if not doubtful effort to find and evaluate additional parameters to characterise further a very low risk group of less than 5% of all breast cancer patients, especially as many questions about the optimal treatment of the remaining 95% are unanswered. Amongst the most urgent unsolved problems is how to identify tumours which hold a high hazard of resistance against or a high chance of response to a given treatment modality or drug. Many of the parameters which have been evaluated for their prognostic significance measure macromolecules important for tumour biology including proliferation, invasion and apoptosis and may gain clinical importance as factors that predict response to therapy (predictive factors). Because unlike prognosis, which is determined by very complex processes that are mirrored by certain histopathological variables known as established prognostic factors (nodal status, tumour size, tumour grade), it is at the molecular level that resistance to therapy occurs.

The first and well established predictive factors are oestrogen and progestin receptor status which indicate the potential response of a tumour to endocrine manipulation. Her-2/neu has gained considerable interest as a new and possibly powerful predictor of response to endocrine and chemotherapy. Some studies suggest that Her-2/neu-positive tumours may be less sensitive to tamoxifen and to cyclophosphamide, methotrexate, 5-fluorouracil (CMF) whilst more sensitive to anthracycline-based therapy [20–22]. However, these associations are not confirmed by other reports [23,24]. Furthermore, a humanised monoclonal antibody against

Her-2/neu has been demonstrated to reduce resistance to several chemotherapeutic regimens [25]. This development opens new perspectives for therapy in that it is preceded only by endocrine treatment as a successful modality to use molecular characteristics of a tumour for selective targeting by recently designed drugs.

Scientific effort should focus on following these routes to improved prediction of chemo- and endocrine resistance and the potential for development of novel therapeutic modalities instead of being diverted by the search for additional prognostic factors with doubtful clinical value.

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