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40 INVITED

Micrometastases in axillary sentinel lymph nodes of breast carcinoma patients

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The very high negative predictive value of axillary sentinel lymph node (SLN) biopsy in staging patients with clinically node-negative breast carcinoma allows almost 65–70% patients to be spared axillary lymph node dissection (ALND) and its associated morbidity because of a metastasis-free SLN. Conversely, in case of a positive SLN biopsy, the standard of care remains completion ALND for a more exhaustive staging. Further axillary involvement, however, will not be identified in the majority of these patients, who will not derive any benefit from axillary dissection. Thus, a predicted small chance of additional axillary metastasis after a positive SLN biopsy might justify avoiding ALND also in a selected cohort of patients with positive SLN biopsy.

The size of SLN metastasis has emerged as a most powerful independent predictor. In particular, patients with micrometastatic SLN (i.e. SLN harboring metastases up to 2 mm in maximum diameter) reportedly are at a significantly lower risk for further axillary involvement than patients with SLN metastases larger than 2 mm (13–24% *vs* 45–79%). The new edition of the TNM classification of malignant tumors has now separately classified patients with isolated tumor cells (ITC) only in the regional lymph nodes within the pN0 (i+) category, and it remains to be determined whether it is meaningful and can be safely adopted also for staging patients undergoing SLN biopsy. In particular, the question now arises whether or not patients with breast carcinoma and ITC only in the axillary SLN are at such a low risk for additional nonsentinel lymph node metastases that completion ALND may not be necessary.

Methods: All the axillary sentinel and nonsentinel lymph nodes of 1228 patients were reviewed histologically, and reclassified according to the current TNM classification of malignant tumors, as bearing isolated tumor cells only, micrometastases or (macro)metastases. The prevalence of metastases in nonsentinel nodes was correlated to the type of SLN involvement and the size of the metastasis, the number of affected SLNs, and the prospectively collected clinicopathologic variables of the primary tumors.

Results: In multivariate analysis, further axillary involvement was significantly associated with the type and size of SLN metastases, the number of affected SLNs, and the occurrence of peritumoral vascular invasion in the primary tumor. A predictive model based on the characteristics most strongly associated with nonsentinel node metastases was able to identify subgroups of patients at significantly different risk for further axillary involvement.

Conclusions: Patients with the most favorable combination of predictive factors still have no less than 13% risk for nonsentinel node metastases and should be offered completion ALND outside of clinical trials of SLN biopsy without back-up axillary clearing.

41 INVITED

Micrometastatic cells as targets for adjuvant therapies

K. Pantel. *Universitätsklinikum Hamburg-Eppendorf, Institute für Tumorbiologie, Hamburg, Germany*

Using monoclonal antibodies to epithelial cytokeratins (CK), individual carcinoma cells can be detected on cytologic preparations at frequencies of 10^{-5} to 10^{-6} (for review, see Pantel et al., Clin. Cancer Res., 2003). Several prospective clinical studies have shown that the presence of CK-positive cells in bone marrow of patients without clinical signs of metastases is prognostically relevant (e.g., Pantel et al., Lancet, 1996; Braun et al., NEJM, 2000; Wiedswang et al., JCO, 2003). In addition to immunocytochemistry, new molecular detection methods based on the amplification of a marker mRNA species by the polymerase chain reaction technique have been developed.

The current assays may be used to improve tumor staging with potential consequences for adjuvant therapy. Another promising clinical application is monitoring the response of micrometastatic cells to adjuvant therapies, which, at present, can only be assessed retrospectively after an extended period of clinical follow-up. In particular for therapeutic monitoring, the analysis of peripheral blood samples is more feasible than the repeated sampling of bone marrow. Several new reliable blood tests are now available and the clinical data obtained with these assays look very promising.

Another important goal is to unravel the biology of the onset of metastasis and search for new therapeutic targets on micrometastatic cells. Our recent expression profiling investigation indicated that hematogeneous micrometastasis in breast cancer is associated with a specific molecular signature of the primary tumor (Woelfle et al., Cancer Res., 2003). The direct analysis of micrometastatic cells in blood and bone marrow is hampered by the low concentration of these cells. The tools established in our laboratory (e.g., micrometastatic cell lines, single cell (RT)PCR, multiple labeling, and FISH) allow to obtain further insights into the phenotype and genotype of single micrometastatic cells. The available data indicate that micrometastatic cells represent a selected population of cancer cells which, however, still express a considerable degree of heterogeneity with regard to chromosomal aberrations and phenotypic properties (Solakoglu et al., PNAS, 2002; Kraus et al., GCC, 2003). Prominent characteristics of micrometastatic cells in blood and bone marrow at the time of primary tumor diagnosis are the lack of proliferation-associated marker proteins (Pantel et al., JNCI, 1993, Offner et al., PNAS, 1999), which may limit the efficacy of adjuvant chemotherapy (Braun et al., JCO, 2000). On the other hand, the frequent expression of the HER2/neu oncogene supports the idea that antibodies or inhibitors directed against this receptor may be useful drugs to eliminate micrometastatic cells (Pantel et al., JNCI, 1993 & 1999; Putz et al., Cancer Res., 1999; Braun et al., Cancer Res., 2001). Interestingly, MHC class I antigens were frequently downregulated (Pantel et al., Cancer Res., 1991), which may limit immunotherapies based on active vaccination against residual tumor cells.

In conclusion, the detection and characterization of micrometastatic cells may improve tumor staging and helps to design new adjuvant therapies to eliminate minimal residual cancer in patients with solid tumors.

Wednesday, 17 March 2004 14:15–15:45

SYMPOSIUM

Psychology and breast cancer: state of the art

42 INVITED

Psychological comorbidity in breast cancer patients

U. Koch, A. Mehnert. *Universitätsklinikum Hamburg-Eppendorf, Institut für Medizinische Psychologie, Hamburg, Germany*

The diagnosis and treatment of breast cancer results in various sequelae in the affected women which can have a considerably negative effect on their quality of life. These include emotional destabilization, an alteration of the physical integrity and self perception, uncertainty regarding social roles and responsibilities, and a modified interactional relationship to their environment.

The present lecture focuses on the issue of psychological comorbidity in breast cancer patients. The relevance of this topic is indicated by evidence which suggests that patients with an additional psychological disorders have a higher risk of morbidity and mortality, a higher risk of chronification

and a lower quality of life, show less compliance, and have longer hospital stays, thus inducing greater costs.

The presentation is based on the one hand on a review of corresponding comorbidity studies from the psycho-oncological research of the past 20 years, and on the other hand on current results from a questionnaire-based study involving more than 1000 breast cancer patients performed at the Institute for Medical Psychology of the Hamburg-Eppendorf University Clinic.

The results indicate a considerable risk of comorbidity for psychological disorders in breast cancer patients. This primarily relates to anxiety disorders and depression, in each of which rates of incidence differing between 10% and 30% have been determined. The frequency of psychological disorders requiring treatment appears to be dependent on numerous factors. In addition to socio-demographic variables, these factors include illness oriented variables such as the stage and prognosis of the illness, the severity of the physical impairment and negative effects on self-perception, as well as psycho-social variables such as the available coping resources, and support from the familial and social environment.

The results show that a qualified treatment of the psychological symptoms (anxiety, depression) is necessary for certain subgroups of breast cancer patients. This can be psychotherapeutic, psychopharmacological, or combined in nature, and requires corresponding specialist training and experience (for example, medical or clinical psychologists or psychiatrists).

A specific problem can be seen however in the fact that the psychological comorbidity in breast cancer patients frequently goes without being recognized by those responsible for primary treatment. This is due in part to the diversity of the psychopathology, the overlapping of somatic and psychological symptoms, the underestimation of psychological disorders in light of dominant physical symptoms, and to the lacking knowledge of the pathology of psychological disorders and their ability to be treated. On this basis, the conclusion can be drawn that oncologists responsible for the primary care of breast cancer patients must be better educated in the diagnosis of psychological comorbidity in the course of their studies and training.

Keywords: Psycho-oncology, psychological comorbidity.

43 INVITED

Psychological response to breast cancer and its impact on survival

L. Fallowfield. *Cancer Research UK, Psychosocial Oncology Group, Brighton, East Sussex, UK*

There have been many attempts over the years to establish the types of pre-morbid personality patterns that either predisposed women to develop cancer or to influence their survival. Findings from much of this early work stimulated considerable interest in the possibility of improving not just the quality but the quantity of women's lives through psychological approaches. In this talk I will briefly review some of the data that both supports and refutes the likelihood that psychological factors influence survival. None of the research findings will impact significantly on most clinicians or clinical care until the complex biological pathways mediating and mind-body interactions are established.

44 INVITED

Who is the patient? Psychological distress of breast cancer couples

L. Baider. *Hadassah University Hospital, Director, Psycho-Oncology Unit, Jerusalem, Israel*

The purpose of this randomized prospective study was to identify factors influencing the psychological distress of breast cancer patients and their husbands during remission. Background variables and distress levels of 172 couples from two populations (Graz, Austria and Jerusalem, Israel) were assessed, using three standardized instruments, during two time periods 6 to 8 months apart. In both geographic-cultural groups, women whose partners refused to participate reported significantly less perceived family support ($P<0.01$ for Graz; $P<0.05$ for Jerusalem). It may be suggested that partner participation serves as an indication of how patients appraise their own perception of family support. The Grand Severity Index (GSI) (measuring total psychological distress) reflected minor changes in psychological distress of both patients and husbands over time. Although findings on the relative distress of healthy partners and patients are not always consistent and are mostly restricted to the first years after diagnosis, the majority of studies support a consistent tendency in the relative but similar psychological distress levels of the patient and spouse. Implications for psychological intervention are discussed.

45 INVITED

Psychological intervention with breast cancer patients: an update

Abstract not received.

Wednesday, 17 March 2004 16:00–17:15

PROFFERED PAPERS

Adjuvant and neo-adjuvant therapy

46 ORAL

Efficacy of Pre-operative Arimidex (anastrozole) compared with Tamoxifen (PROACT) as neoadjuvant therapy in postmenopausal women with hormone receptor-positive breast cancer

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Background: In selected patients both cytotoxic and endocrine treatments (eg tamoxifen) given for a short period prior to breast cancer surgery have been shown to cause tumour shrinkage. This enables mastectomy, where a tumour was previously considered inoperable, or breast conserving surgery (BCS) when only a mastectomy was feasible prior to treatment.

Materials & Methods: The PROACT trial evaluated the efficacy of anastrozole (AN) versus tamoxifen (TAM) as neoadjuvant therapy in postmenopausal women with large, operable or potentially operable, locally-advanced, hormone receptor-positive breast tumours. Patients were randomised to double-blind treatment for 12 weeks prior to surgery. Additional chemotherapy was optional and was decided prior to randomisation. The primary objective was a comparison of objective response (OR) rates as assessed by ultrasound at 12 weeks. Secondary objectives included changes in both planned and actual surgery (inoperable at baseline to mastectomy/BCS, or mastectomy at baseline to BCS) from baseline to 12 weeks and tolerability.

Results: 451 patients (mean age 67 years) were randomised to treatment with AN (n=228) or TAM (n=223). At baseline, 14.2% of the patients had tumours assessed as suitable for BCS, 78.3% for mastectomy and 7.3% had inoperable tumours. OR rates by ultrasound are shown in table 1.

Table 1

Patient population	N	OR (% patients)			
		AN	TAM	Odds ratio (95%CI)	P value
All patients	451	39.5	35.4	1.24 (0.84–1.83)	0.29
Hormonal therapy only	314	36.2	26.5	1.57 (0.97–2.55)	0.07
Hormonal therapy +*	262	36.6	24.2	1.81 (1.06–3.11)	0.03

*Also requiring mastectomy/inoperable at baseline.

Considering those patients receiving hormonal therapy alone, more of the AN than TAM treated patients had an improvement in their planned surgical option (47% versus 38% respectively, 1.44 [0.88–2.36] p=0.15) and significantly more of the AN treated patients had an improvement in their actual surgery (43% versus 31% respectively, 1.69 [1.01–2.81] p=0.04). Both treatments were well tolerated.

Conclusions: AN is an effective and well-tolerated neoadjuvant treatment for postmenopausal women with hormone receptor-positive breast cancer whose large tumours necessitate a mastectomy or who have locally-advanced, inoperable disease. These data are consistent with previous findings for AN.

47 ORAL

Anastrozole versus tamoxifen as neoadjuvant therapy for oestrogen receptor-positive breast cancer in postmenopausal women: the IMPACT and PROACT trials

I. Smith[1], L. Cataliotti[2]. *On behalf of the IMPACT and PROACT Trialists.* [1]*Royal Marsden Hospital, London, UK;* [2]*University degli Studi di Firenze, Firenze, Italy*

Background: Two large trials have evaluated anastrozole (AN) vs tamoxifen (TAM) as neoadjuvant therapy in postmenopausal women with hormone-sensitive breast cancer. In contrast to most previous randomised neoadjuvant trials, patients eligible for breast-conserving surgery (BCS) at entry were included. The PROACT (PReOperative Arimidex (anastrozole) Compared with Tamoxifen) trial (N=451) evaluated AN vs TAM, while the IMPACT (IMmediate Preoperative Arimidex, tamoxifen or Combined with Tamoxifen) trial (N=330) compared AN vs TAM alone and in combination.