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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

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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

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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