6 Proffered paper oral

Impact of Neoadjuvant Systemic Treatment and Prior Surgery On Sentinel Lymph Node Detection − Results From the Prospective German Multiinstitutional SENTINa Trial

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Background: For patients with breast cancer undergoing preoperative / neoadjuvant systemic treatment (NST) the optimal timing of sentinel lymph node biopsy (SLNB) is still unclear. Evidence for both feasibility (detection rate, DR) and reliability (false negative rate, FNR) of SLNB is limited and derived only from monocentric and/or retrospective data.

Material and Methods: The SENTINA trial (SENTinel NeoAdjuvant) is a 4-arm prospective multicenter cohort study designed to examine the DR and FNR of a standardized SLNB-procedure in the neoadjuvant setting. In this first analysis, we present data on sentinel lymph node (SLN) detection rates in patients with breast cancer before and after NST. In SENTINA, patients were categorized into four treatment arms according to axillary staging results before and after NST. Patients with a cN0 status underwent SLNB prior to NST and were categorized as arm A and B: If the SLN was histologically negative no further axillary surgery was performed after NST (arm A), whereas in case of histologically positive SLN status, a second SLNB and AD was performed after NST (arm B). Patients with a cN1 status prior to NST underwent no axillary surgery prior to NST and were stratified as arm C and D: If patients converted to cN0 after NST, SLNB and AD were performed (arm C); patients presenting with cN1 status after NST underwent classical AD (arm D).

Results: 1240 patients from 104 institutions entered the trial. 804 women had clinically negative lymph nodes and received SLNB prior to NST (arm A/B). Among these, 284 patients (34.5%) had histologically involved nodes and underwent a second SLNB followed by AD after NST (B2). 436 patients, who presented initially with suspicious nodes and converted to a cN0 status after NST (arm C) received SLNB without any prior axillary surgery. The SLN detection rate was 99.1 % (798/805) in arm A/B and 81.9% (357/436) in arm C. For patients with a positive SLN in arm A/B who received a second SLNB after NST the detection rate was no more than 62.3 % (177/284). The difference between the detection rates of these three groups was highly statistically significant ($p < 0.001$).

Conclusion: The SLN detection rate in patients with breast cancer is highly dependent on prior systemic and/or surgical treatment. The SLN detection rate in patients converting from a clinically positive to a clinically negative axilla status through NST is significantly lower compared to patients with an a priori clinically negative axilla. Both, however, are yet significantly higher compared to patients who receive prior surgery and systemic treatment before SLNB is performed.

7 Proffered paper oral

Relevance of Breast Cancer Subtypes in Response Monitoring with 18F-FDG PET/CT During Neoadjuvant Chemotherapy

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Background: Neoadjuvant chemotherapy (NAC) is increasingly applied in stage II and III breast cancer. Response monitoring with magnetic resonance imaging (MRI) has been shown valuable, but knowledge of the breast cancer subtype is essential for correct interpretation of response assessment. The aim of the present study was to evaluate the relevance of breast cancer subtype for ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography with computed tomography (PET/CT) markers for monitoring of therapy response during NAC.

Methods: Evaluation included 98 women with primary stage II or III breast cancer. FDG PET/CT scans were performed before and after six weeks of NAC using similar prone patient positioning. FDG uptake of the primary tumor was quantified using maximum standardized uptake values (SUVmax). Tumors were divided into three subtypes using immunohistochemistry: human epidermal growth factor receptor 2 (HER2) positive, estrogen receptor (ER) positive/HER2 negative and triple negative. Tumor response was assessed as presence of residual tumor in the surgery specimen (no response or partial response) or absence thereof (near complete or complete response). Multivariable regression analysis and receiver operating characteristic (ROC) analyses were employed to determine significant associations.

Results: A (near) complete response at pathology was observed in 19 (76%) of 25 HER2 positive tumors, 7 (16%) of 45 ER positive/HER2 negative tumors and 20 (71%) of 28 triple negative tumors. In the multivariable regression analysis, (near) complete response in the surgery specimen was significantly associated with relative reduction of SUVmax of the tumor between both scans and breast cancer subtype (area under the curve of the ROC curve 0.85 [95% confidence interval 0.77–0.93], $p < 0.001$); no significant associations were found for FDG uptake at baseline and age. In a subgroup analysis of breast cancer subtype, a significant association was found between pathologic response and relative reduction of SUVmax for ER positive/HER2 negative and triple negative tumors ($p = 0.003$ and $p = 0.009$, respectively), but not for HER2 positive tumors ($p = 0.192$).

Conclusion: Knowledge of the breast cancer subtype appears relevant for the assessment of response to NAC with FDG PET/CT. Response monitoring with FDG PET/CT may predict a pathological response adequately in ER positive/HER2 negative and triple negative tumors, but seems less accurate in HER2 positive tumors. The reasons for these differences need to be elucidated in further investigations.

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CLINICAL SCIENCE SYMPOSIUM

Resistance to Hormonal Therapy

8 Invited

Overview of Mechanism of Resistance in Hormonal Therapy

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The estrogen receptor (ER) is a key regulator of breast cancer (BC) biology and is expressed in almost 75% of breast cancers. Targeting ER has been the focus of endocrine treatment strategies developed during the last decades. ER selective modulators or downregulators (i.e. tamoxifen or fulvestrant), and inhibitors of estrogen synthesis (i.e. aromatase inhibitors) are among the most successful targeted agents ever developed for cancer. Due to their excellent activity and tolerability, these agents have significantly improved the management of ER positive disease. However, at least 25% of patients in the adjuvant setting and all patients in the advanced setting develop resistance to hormonal therapy after a variable period of time. Therefore, endocrine resistance accounts for a large fraction of therapeutic failures in BC each year resulting in millions of deaths worldwide.

Biological mechanisms of endocrine resistance seem to often rely on altered ER pathway function rather than reduced ER levels. As the complex ER biology can be physiologically modulated by a number of signalling pathways, deregulation of such pathways has been historically recognized as a major driver of endocrine resistance. The paradigm of such interaction is hyper activation of the Epidermal Growth Factor Receptor family members EGFR and HER2 that have been shown to modulate ER phosphorylation and activation, co-factors recruitment and, ultimately, response to endocrine treatment. Other relevant pathways such as the IGF1R, PI3K/Akt, p44/42 MAPK and stress activated protein kinases (JNK and p38 MAPK) have been associated to endocrine resistance by means of their crosstalk with ER and, possibly, by inducing a shift in ER function towards cooperation with other transcription factors such as AP-1. Recent clinical data showed for the first time that modulation of such pathways in combination with endocrine therapy can improve patient outcomes. From a prospective standpoint, these data serve to clinically validate the concept that complete ER blockade is achieved by targeting not only ER but also its relevant signalling partners. As new biologic information on ER activity translates into innovative therapeutic approaches, a number of signalling inhibitors are in pre-clinical and clinical development for this subset of patients. Due to the clinical importance of this issue, scientific