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The molecular classification of breast cancer according to the stem-cell model provides important informations for systemic adjuvant treatment decision

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Background: The link between the estrogen receptor (ER) and tumor growth belongs to the fundamentals of endocrine responsiveness of breast cancer. A negative association of ER expression and proliferation has been documented for normal breast but seem to differ for breast cancer subtypes descended from distinct progenitor cells. Despite the growing evidence of the stem cell concept for breast cancer there are no data in terms of therapy benefit of those tumors.

Material and Methods: We compared the link between ER expression and proliferation in breast cancers with stem cell like features and more mature types. Affymetrix microarray data of more than 1300 breast cancer samples were stratified using the expression of a Stem Cell Like (SCL) signature of coordinatively expressed genes containing stem and progenitor cell markers as e.g. CK5/6, CK14, ITGA6 and CD133.

Results: A conserved inverse link of ER and Ki67 expression as a surrogate for proliferation among SCL+ tumors (n = 357/1369 [26 %]) allowed the delineation of those ER positive tumors in the Non-SCL group where this link is uncoupled. Uncoupling was observed for about one third of all breast cancers. These tumors were characterized by a prognosis inferior to the ER negative cancers despite an apparent positive ER status with lower 5 and 10 year survival rates (HR: 2.05; 95% CI 1.61−2.61; P < 0.0001). Tumors were subsequently stratified for different forms of systemic therapy (none, endocrine or cytotoxic treatment) and analyzed regarding their follow up data.

Since high proliferation is commonly used as a predictor of the effectiveness of cyctoxic therapy, we analyzed if there are differences between SCL and Non-SCL tumors stratified according to their proliferative state. Furthermore the efficacy of endocrine treatment in high or low proliferating ER positive tumors is a matter of question for adjuvant treatment decision.

In addition to prognostic data, the predictive value of tumor classification according to stem cell like features will be discussed at the meeting.

Conclusion: Classification of breast cancers according to the expression of stem/progenitor cell markers identifies clinically relevant tumor groups. The observed uncoupling of the link between ER and proliferation suggests an influence on the response to endocrine therapy with important implications.

However, whether uncoupled tumors require a different type or a more aggressive therapy is not yet clear and will require future work.

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Incremental costs of chemotherapy – Pharmacoeconomic results from the prospective adjuvant WSG-AGO Intergroup EC-DOC trial comparing an anthracycline–docetaxel sequence to CMF in node-positive breast cancer

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Background: Taxane based adjuvant chemotherapy is the current standard for patients with node positive breast cancer. Compared to the older standard CMF or anthracycline containing regimens, the increase in efficacy is significant but modest. Next to clinically relevant side effects, the implementation of taxanes is associated with a relevant burden on health care resources. In the present study, we compared a modern taxane-based sequential regimen (4 × epirubicin/cyclophosphamide followed by 4 × docetaxel q21, EC-DOC) to the low-priced and less toxic CMF in patients with primary node positive breast cancer with special consideration of costs and resource consumption.

Materials and Methods: Data on resource consumption were obtained between 3/2000–5/2002 alongside the prospective, randomized, multicenter phase III WSG-AGO Intergroup trial (2000–2005) comparing EC-DOC to CMF or FEC. Total costs were presented from hospital provider perspective.

Results: A cohort of 110 patients from 38 study centers receiving a total of 1047 chemotherapy-cycle days was analyzed. The mean patient age was 52.4 years. Mean direct costs for the EC-DOC group (n = 54) totaled €8,459 per patient (95% CI: €7,785−9,132) with costs for cytostatics being the largest burden (€5,673, i.e. 67%). In contrast CMF was significantly less expensive (−41.2%) with mean costs of €4,973 (95% CI: €4,706−5,240). Rehospitalisation associated to toxicity was reduced by half in the CMF group (CMF: n = 4, EC-DOC: n = 8).

Conclusions: Our results picture a substantial budget increase attributable to introduction of taxanes to adjuvant chemotherapy of early breast cancer. The provided data will allow health economic evaluations in the context of modern individualized chemotherapy strategies.

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Extended adjuvant (EA) endocrine therapy – Tamoxifen (TAM) or an aromatase inhibitor (AI)?

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Background: The second 5 years after TAM therapy for hormone-sensitive breast cancer is associated with a rate of relapse of about 10% (node-negative), 16% (1−3 positive nodes), and 32% (4−9 positive nodes). Previous studies have shown that TAM use >5 years was not efficacious, and this is currently not recommended. MA.17, ABCSG, and NSABP B-33 explored EA therapy (EAT) with AIs, and ATLAS explored EAT with TAM. Preliminary results from ATLAS found that EAT after 5 years of TAM reduces late recurrence risk, which may now raise questions of the appropriate EAT (AI or TAM).

Methods: Results from the 2 large randomized trials (MA.17 and ATLAS) were compared. MA.17 randomized 5187 postmenopausal women who completed 5 years of TAM with 5 years of letrozole (LET) or placebo (PLA). The primary endpoint was disease-free survival (DFS). ATLAS randomized approximately 11,500 patients who completed 5 years of TAM to a further 5 years of TAM or not (control). Mortality and recurrence, including contralateral breast cancer, were assessed.

Results: At 30 months' median follow-up (FU) in MA.17, LET was associated with significantly improved disease-free survival (DFS) (hazard ratio [HR] = 0.58) and distant DFS (DDFS; HR = 0.60) vs PLA, and LET was found to be safe and well tolerated. At 50.4 months' mean FU in ATLAS, TAM was associated with a significantly lower recurrence rate vs control (HR = 0.87). There was no significant difference in overall survival in either trial. DDFS and toxicity were not reported in ATLAS and thus cannot be compared with MA.17 results.

Conclusions: Hormone-positive breast cancer is associated with a high rate of late relapse, and extending the duration of adjuvant therapy is beneficial. Adverse events (AEs) have not been reported for ATLAS, but previous studies of the long-term use of TAM have been associated with serious AEs. Particularly in postmenopausal women who are eligible for AIs, the risk-benefit ratio does not justify using TAM >5 years without further safety data, but ATLAS provides further rationale for EAT. A 40% DDFS improvement with EAT LET should translate into improved patient outcomes. After 5 years of TAM, EA LET is safe and associated with a greater reduction in late relapse risk and appears to offer a greater benefit than 5 additional years of TAM.

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Expression of estrogen receptor (ER) in disseminated tumor cells of breast cancer patients

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Background: The presence of disseminated tumor cells (DTC) in bone marrow (BM) of primary breast cancer patients is associated with poor prognosis. These patients may benefit from adjuvant endocrine therapy since cytotoxic agents are not able to eliminate DTCs completely as previously shown. The ERα status is routinely defined in primary tumor tissue and only patients with hormone receptor positive breast cancer are eligible for hormonal treatment. However, the ERα status of DTC may differ compared to the primary tumor. Therefore, the aims of this study were (1) to determine the ERα status of DTC in BM of breast cancer patients, and (2) to compare the ERα status of DTC and corresponding primary tumors.