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Basal-like subtype of breast carcinoma predicts poor clinical outcome in patients with high-risk breast cancer treated with high-dose (HD) or dose-dense chemotherapy: Results of multivariate analysis from the WSG-AM-01 phase III trial

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Introduction: Dose intensification strategies and especially adjuvant high dose chemotherapy in high-risk breast cancer are controversial. Prognostic and predictive factors identifying patient subgroups with maximal benefit from high-dose chemotherapy with peripheral blood stem cell transplantation (PBSCT) remain to be defined. We retrospectively evaluated the role of molecular markers especially those defining basal-like type of breast cancer (negative hormone receptors (HR), not overexpressing HER-2/neu, positive for basal cytokeratins such as Ck5, MIB and c-kit).
Methods: 403 patients were randomly assigned to dose-dense conventional chemotherapy (four cycles of EC, followed by three cycles of CMF q2w) or to two courses of EC followed by two courses of HD chemotherapy (EC-thiotepa) with PBSCT. Treatment arms were well balanced for age, menopausal status, tumour size, grading, number of involved lymph nodes, nodal ratio and hormone receptor status. A multivariate analysis was done in 239 patients, where paraffin-embedded tumors were assessable for central pathologic review including grading. Ck 5, HR, c-kit, p 53, MIB, HER-2/neu, bcl-2, Cyclin D1, p 16, E-Cadherin in these tumors were detected by immunohistochemistry.
Results: Within the WSG AM01 trial the average number of positive axillary lymph nodes was 17.6. At a median follow-up of 48.6 months there is a significant overall survival benefit for patients receiving HD. Ck5 status was available from 224 tumours (20 Ck5+/204 Ck5−). Ck5 positivity was associated with high grading ($p < 0.0001$), ER− ($p \leqslant 0.0001$), PR-($p = 0.0002$), p 53 ($p = 0.003$), c-kit ($p = 0.0007$), p16 ($p < 0.0001$) and MIB ($p = 0.0005$). In the multivariate analysis patients with Ck5 positive tumors had a poor outcome (HR for OS = 3,441 [CI: 1.51−7.67], $p = 0.0031$) independent of therapy, stage and nodal status. Other factors associated with poor outcome in the multivariate analysis were over expression of HER-2/neu ($p = 0.0089$), PR negativity ($p = 0.021$), tumor size ($p = 0.028$), MIB positivity ($p = 0.038$).
Interpretation: The retrospective evaluation of prognostic factors from other high-dose chemotherapy trials are highly controversial. HER-2/neu, age and grading are the best documented prognostic and/or predictive factors. Our data suggest that basal-type breast cancer correlates with poor outcome. Further analysis by treatment arm will be presented.

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Time to response – a comparison of fulvestrant with anastrozole

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Background: It has been speculated that pharmacokinetic differences between treatments may affect the observed time to response (TTR) in advanced breast cancer. Since fulvestrant is administered as a sustained release intramuscular (IM) injection, which takes 3 to 6 months to reach steady state, there is a concern amongst physicians that this may result in a delayed time to response compared with aromatase inhibitors.
Materials and methods: TTR data were collected from two Phase III trials (0020 and 0021) of fulvestrant 250 mg/month (intramuscular injection) versus anastrozole 1 mg/day (orally) in the treatment of postmenopausal women with advanced breast cancer who had recurred or progressed on prior tamoxifen therapy. Combined analysis of data from both trials was performed to determine median TTR with each treatment. Median TTR was calculated from randomisation to the observation of an objective response (complete or partial).
Results: The time taken to achieve an objective response was similar with fulvestrant and anastrozole (Table). Median TTR with fulvestrant was close to 3 months and almost identical to that of anastrozole, but values ranged between 0.9−33.1 months overall, suggesting that an objective response may still occur after a long period of stable disease with fulvestrant treatment.

	TTR (months)	
	Median	Range
Fulvestrant 250 mg/month (n = 82)	3.10	0.9−33.1
Anastrozole 1 mg/day (n = 70)	2.99	0.7−20.2

Data source: Combined data (Trials 0020 and 0021)

Conclusions: Median TTR was similar between fulvestrant and anastrozole. These data suggest that patients without rapidly progressive disease should be kept on endocrine treatment for at least 3 months to allow a response to be achieved prior to considering changing treatments. Furthermore, objective responses may occur following a long period of stable disease during fulvestrant treatment.

Poster presentations (Tue, 1 Nov)
Breast cancer – basic science, molecular predictive assays, translational research

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Co-expression of P27 kip1/p21 is an independent indicator of good prognosis in lymph node positive breast carcinomas

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Progression through the cell cycle is controlled by the cyclin-dependent kinases (Cdks), allowing repair of damaged DNA, and preventing its replication or the loss of genetic material. The kinase inhibitor proteins (KIPs) p27 kip1 and p21 Waf1 negatively regulate cell cycle progression by preventing the passage of cycling cells from G1 to S phase. This occurs via activation of G1 cyclin-dependent kinases, which are thought to play a role in tumour suppression. However, evidence is conflicting as to whether p27 kip1 and p21 Waf1 have a significant role to play in breast cancer.
Material and methods: The present investigation included 710 breast cancer cases with a median follow-up of 87 months, in order to determine the prognostic significance of p27 kip1 and p21 Waf1. Immunohistochemical analysis of tissue microarrays was used to assess expression of these markers. These specimens comprise a well characterized series of patients (70 years of age or less, mean: 54) with primary operable breast cancer diagnosed between 1987 and 1992.
Results: Univariate analysis showed a significant association between reduced p27kip1 expression and increasing tumour grade ($p < 0.001$), development of distal metastasis ($p = 0.012$) and tumour recurrence ($p = 0.014$). A further association was noted between reduced p27 kip1 and ductal/no special type tumours ($p = 0.008$). Survival analysis demonstrated that patients with tumours with high p27 kip1 levels had an improved survival compared with those with low expression (log rank = 0.006). Reduced p21Waf1 expression was noted in high grade tumours ($p = 0.02$) and poor prognosis tumour types ($p = 0.05$), however, no correlation was observed with survival. On multivariate analysis, using the Cox regression in lymph node positive patients, the combination of a p21(+)/p27(+) phenotype was independently associated with a good prognosis (HR 3.338, 95%CI: 1.215−9.168, $p = 0.019$).
Conclusion: It is concluded that lymph node positive breast cancer patients with a p21(+)/p27(+) phenotype demonstrate prolonged survival times, and that this is independent of other factors such as tumor size and grade. This may indicate a subset of patients for whom less aggressive adjuvant therapy is appropriate.

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The analysis of ATM mutations in high-risk breast cancer patients

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Background: Ataxia-telangiectasia (A-T), caused by mutations in the ATM (A-T mutated) gene, is an autosomal recesive disorder characterized by cerebellar ataxia, oculocutaneous telangiectasia, immunologic deficiency, hypersensitivity to ionizing radiation and predisposition to cancer. The finding that heterozygous mutation carriers (0.5−1% of the general population) have an increased risk for breast cancer (BC) was supported by numerous studies. The purpose of this study was to analyze the occurrence of ATM mutations with hereditary breast cancer.
Material and methods: Patients from high risk breast and/or ovarian cancer families that had previously been screened for mutations in BRCA 1 and BRCA 2 genes were analyzed for the presence of truncating ATM mutations. RNA was isolated from peripheral blood lymphocytes and reverse transcribed to cDNA. The coding sequence of ATM was amplified in 7 overlapping fragments. PTT was used for pre-screening of amplified fragments; the final analysis of identified gene alterations was done by sequencing.
Results: In a group of 70 high-risk families, the c.5932G>T nonsense mutation, which results in a termination of translation at codon 1978, was