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Detection of tumor stem cells among circulating epithelial tumor cells (CETC) and relationship to therapy response.

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Background: It has been shown that the metastatic process is highly inefficient. Thus in the experimental setting, using breast cancer cell lines, only 0,1 to 0.01% of the injected cells are capable of forming metastases. With respect to cells released from primary tumors it is neither known, how many cells survive in the circulation nor what proportion is capable of forming metastases. Therefore we have attempted to determine the fraction of stem cells among the CETC and to correlate their frequency to relapse.

Material and Methods: Tumor cells were quantified with an automated microscope (Laser Scanning Cytometer®, Icis or ScanR) from anticoagulated blood drawn before each new therapy cycle from patients treated with systemic chemotherapy after surgery and subsequent maintenance therapy. After red blood cell lysis leucocytes were stained with PE-anti-CD45 and tumor cells with FITC-anti-EpCAM. Tumor stem cells were tried to define in 2 ways: 1. Using PE-conjugated anti-CD24 Epithelial antigen positive cells were counterstained and the CD24 negative cells determined. 2. Using the Aldefluor method epithelial cells staining intracellularly positive were determined and changes registered as % increase or decrease. The response to therapy was correlated to outcome.

Results: Both methods were well applicable. With the anti-CD24 counter stain, most CETC stained positively. A minor fraction of less than 1% of CETC was lacking CD24 staining and was regarded as the CD24 negative stem cell population. With regard to the Aldefluor method, both green fluorescing FITC anti-CD326 and red fluorescing Dye-anti-CD326 were used for screening of CETC and subsequently green intracellular fluorescence was determined inside the CETC. Aldefluor positive CETC also were in the range of 1%. Patients with CETC increasing during systemic chemotherapy which are defined as poor prognosis patients are now investigated for their proportion of stem cells during CETC increase.

Discussion: These analyses will help to clarify whether an increase in CETC during systemic chemotherapy is due to tumor stem cells, surviving conventional chemotherapeutic agents and whether they might be susceptible to new agents.