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Circulating cancer cells and their use in the real life

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CTC's are cancer cells of solid tumor origin found in the peripheral blood of patients with advanced stages of most types of solid cancers. CTC's are very rare and represent a surrogate biomarker of hematogenous metastases. Disseminated cancer cells (DTC's) represent post-extravasation phase and can be found in bone marrow. DTC/CTC detection therefore can be used as a strong prognostic factor, so called minimal residual disease. CTCs have procoagulant phenotypes and strongly determine local thrombin concentration leading to risk of developing thrombosis. CTCs also interfere with host immune cells and platelets which release angiogenic and growth factors (VEGF, PDGF, TGF-beta) what lead to tumor growth and establishment of metastatic tumor sites. CTCs express hypoxia-inducible factor 1 α (HIF-1 α), vascular endothelial growth factor (VEGF), and VEGF receptor (VEGFR2), associated with angiogenesis and tumor progression. CTCs detection is an independent, strong prognostic factor for Overall Survival (OS) and predictor of Progression Free Survival (PFS) in patients with metastatic breast cancer, prostate cancer and advanced colorectal cancer. The standardized method for detection CTC in blood is an automated immunomagnetic enrichment and staining system for CTCs (the CellSearch[®] system). It performs automated immunomagnetic epithelial cell adhesion molecule (EpCAM)- based enrichment followed by CK staining of CTCs in blood samples. The main target organ for the metastatic process in colon cancer is liver. Therefore the portal flow can represent a "post-intravasation highway" for CTC's. Meta-analysis of nine studies that used molecular detection (646 patients) concluded that CTC's detection in portal flow correlate with nodal invasion, and that CTC's status during surgery for primary tumor correlate with further liver metastatic relapse, nevertheless of tumor stage. Also, in other gastrointestinal carcinomas, presence of CTCs means worse prognosis. CTCs can estimate the risk of metastating disease (prognostic information), and identifying therapeutic targets (diagnostic information) and resistance mechanisms. CTCs is perfect alternative to invasive biopsies for early detection of metastatic tumor tissue, and to better assess responses to treatment (liquid biopsy). Molecular profiling of CTCs has the potential to provide individualisation of cancer therapy. Most of the current strategies for detecting CTC are based on the epithelial markers, epithelial cell adhesion molecule and keratin; however, in certain tumor types, these epithelial markers are downregulated during tumor cell dissemination, hampering the detection of CTCs. The optimal cut-off for the number of CTCs associated with worse prognosis is still not established. Low number of CTCs is also restriction for proper evaluation of therapy response. The fact that described patients with breast cancer dormancy who had detectable CTCs had not relapsed even after a follow-up of >20 years makes the potential benefit of this tool questionable. Also, if patient has two cancers (breast, colorectal), one or both can be metastatic; than the interpretation of CSCs results is regardless of origin of the disease. CTC's presence during treatment also means that it's a cancer with primary resistency for therapy. Shall we stop harmful and unusefull therapy? Can we define subpopulation of patients with the highest treatment benefit trough the CTCs measurements? Does procoagulant nature of CTCs has impact on cancer progres? Is cancer-response on anticancer therapy also related to antithrombotic therapies? Key to answer these and many other questions is in the incorporation of CTCs into prospective clinical trials to test their clinical utility and there is no doubt that CTCs can become usefull diagnostic and prognostic tool for patients with cancers. We can conclude that CTCs will provide new insight into the biology of cancer and the process of metastasis.

Biography

Renata Dobrila-Dintinjana is engaged in field of gastrointestinal cancers and Supportive Cancer Care for 20 years and she has authored more than 50 peer-reviewed articles and over 100 reports. She is author of ten book chapters, reviewer for couple of international journals (*J of Supportive Cancer Care*,) and international projects in field of Cancer Research. She is also invited speaker in Postgraduated Courses regarding abdominal malignancies (Hong Kong, Moscow) and in many International Congresses and Symposia. She is member of several National Scientific Committees regarding Gastrointestinal Cancer and Supportive Cancer Care. She is serving as co-editor of *Journal of Hepato-Gastroenterology* and is Coordinator for Oncology section of IASGO.

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