Circulating cell-free DNA as a new tool for personalized pharmacotherapy

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Scope of the lecture:

The lecture will address key issues regarding the use of circulating tumor DNA as a liquid biopsy for molecular monitoring of chemo/immunotherapy in cancer as well as the use of biomarkers to monitor graft integrity and to personalize immunosuppression in solid organ transplantation. The rationale for using graft-derived cell-free DNA as a biomarker in transplantation will be explained and selected results of clinical studies in kidney, heart, lung and liver transplantation will be presented.

Learning objectives:

1. Use of cancer pharmacogenomics for the prediction of efficacy of molecular targeted therapy
2. Application of circulating cell-free DNA as a liquid biopsy in cancer and transplantation
3. Use of graft-derived circulating cell-free DNA for the detection of rejection episodes in transplantation early, at an actionable stage

Extended abstract:

High-quality genomic analyses are essential for a precision medicine approach to cancer patient management[1]. Genome sequencing can identify the molecular abnormalities that predict either good or poor outcomes and identify new targets for therapy. In genotype-directed cancer care, traditional biopsy-based approaches have limitations, in particular when re-biopsies are needed to characterize resistance to targeted therapies. Noninvasive genotyping of circulating cell-free tumor DNA (ctDNA) in plasma as a “liquid biopsy” is an alternative method for personalizing therapy of genotype-defined solid tumors. Serial quantification of plasma genotype has allowed detection of resistance mutations up to 16 weeks before radiographic progression. Tumor-specific genomic alterations identified in cell-free DNA (cfDNA) from patient blood samples seem to be helpful to monitor relapse or response to treatments. ctDNA quantification techniques include sequencing of plasma DNA, droplet digital PCR, and other quantitative allele-specific PCR methods. It has been demonstrated that blood is a good substitute to guide EGFR tyrosine kinase inhibitors (TKIs) treatment when tumor tissue is unavailable or insufficient for testing *EGFR* mutations. In May 2016, the FDA approved the first such liquid biopsy test for the detection of *EGFR* gene mutations in NSCLC. In patients with metastatic breast cancer, circulating tumor DNA showed a better correlation with tumor burden and was an earlier measure of treatment response compared to both CA 15-3 and circulating tumor cells. Noninvasive analysis of ctDNA allows for identification of specific mutations selected by TKIs treatment such as *EGFR* T790M or C797S in patients with NSCLC. ctDNA is also useful for the detection of the *KRAS* G12V mutation in colorectal cancer patients and of *BRAF* V600E/V600K mutations in melanoma patients. Gains and losses of chromosomal regions (copy number aberrations) have been detected in tumor-specific plasma cfDNA and can be used to compute a genomic copy number instability score (CNI) of cfDNA. CNI change may serve as an early

predictor of therapeutic response in many cancer types (e.g. NSCLC, colorectal cancer, pancreatic ductal adenocarcinomas, oropharyngeal cancers). Recently, it has been shown that the CNI score predicts response to immunotherapy. In patients with head and neck cancer, the CNI score was superior to clinical parameters for prediction of recurrence-free survival. Use of such personalized diagnostics has gained ground in cancer care, but challenges remain.

Molecular biomarkers have attracted special attention in transplantation because of the still unresolved problems that limit long-term outcomes. Biomarkers are especially needed that can be used to facilitate personalized immunosuppression. Therapeutic drug monitoring and conventional laboratory tests are not useful for the early detection of acute rejection. A particularly promising new approach for the early detection of graft rejection is based on the determination of graft-derived circulating cell-free DNA (GcfDNA).[2] Numerous independent studies have shown that GcfDNA can be used to detect organ damage from rejection episodes early, at an actionable stage, and is a more reliable marker of graft injury compared to conventional organ function tests. For example, in a prospective multicenter cohort study in liver transplantation GcfDNA values were about 9-fold elevated in 17 patients during biopsy proven acute rejection episodes compared to 88 patients during stable periods.[3] Values were already elevated 7-15 days prior to the clinical diagnosis of rejection. In another study, 19 cardiac recipients with acute biopsy proven rejection had about 6-fold higher GcfDNA test results compared to 66 apparently stable patients. Values were already elevated 9-30 days prior to the diagnosis of acute rejection in 14 patients. There was only a low correlation of GcfDNA with hs-Troponin I (r=0.50). Similar promising results have also been published for kidney and lung transplantation. GcfDNA may also be useful to guide changes in immunosuppression and to monitor immunosuppression minimization. In summary, this molecular approach promises to allow more personalized treatment that shifts emphasis from reaction to prevention, provides actionable healthcare information and improves outcomes at lower healthcare costs.

1. Oellerich M, Schütz E, Beck J, Kanzow P, Plowman PN, Weiss GJ, Walson PD. Using circulating cell-free DNA to monitor personalized cancer therapy. Crit Rev Clin Lab Sci 2017; 54: 205-218.

2. Oellerich M, Walson PD, Beck J, Schmitz J, Kollmar O, Schütz E. Graft-derived cell-free DNA as a marker of transplant graft injury. Ther Drug Monit 2016; 38 (Suppl 1); S75-S79.

3. Schütz E, Fischer A, Beck J, Harden M, Koch M, Wuensch T, Stockmann M, Nashan B, Kollmar O, Matthaei J, Kanzow P, Walson PD, Brockmöller J, Oellerich M. Graft-derived cell-free DNA – a noninvasive early rejection and graft damage marker in liver transplantation: a prospective observational multicenter cohort study. PLOS Med 2017; 14: e1002286; doi: 10.1371/journal.pmed.1002286.