Perspectives in Clinical and Medical Cytomics: Individualized Pretherapeutic Risk Assessment for Diffuse Large-B-Cell Lymphoma and Acute Myeloid Leukemia (AML) Patients

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Background: Diseases represent molecular alterations in cellular systems (cytomes). Cytomics as the analysis and evaluation of multimolecular changes in heterogeneous cytomes may provide predictive or diagnostic information on diseased patients as well as an individualized risk assessment (Valet G, JBRHA (2002) 16:164-167). Individualized risk assessment by data pattern analysis is distinguished from statistical prognosis evaluation where individual molecular or clinical parameters are typically related to disease progression or outcome of larger patient groups.

Goal: Individualized risk assessment for diffuse large-B-cell lymphoma patients by CLASSIF1 data pattern analysis (http://www.biochem.mpg.de/valet/classif1.html) using data from A. Rosenwald et al. NEJM 346:1937-1847(2002) as well as for AML patients using data from the AML'96 multicenter study of the Süddeutsche Hämoblastosegruppe.

Methods: Files: DLBL_patient_data_NEW.txt and NEJM_Web_Fig1data.html from http://llmpp.nih.gov/DLBCL contain patient information and risk indices as well as 7399 gene expression profiles for 160 learning set patients, 80 validation set patients, 36 further lymphoma patients and 19 gene expression profiles of CLL patients, B-cells and transformed cell lines. The gene array data were subjected to CLASSIF1 data pattern analysis (http://www.biochem.mpg.de/valet/classif1.html). Pretherapeutic AML patient risk assessment was obtained from clinical (n=15), malignant immunophenotype (n=36) and cytogenetic (n=25) parameters of 724 patients.

Results: Predictive values of 96.1% for non-survival and 66.3% for survival were determined for large-B-cell lymphoma patients of the learning set together with 78.3% and 45.4% for patients of the unknown test set. The discriminatory data pattern contains 12 genes. Indicators for high risk non-survivor patients were increased expression of ATP synthase (Hs.25), adenine phosphoribosyltransferase (Hs.28914), nuclear receptor co-repressor 2 (Hs.287994) and of genes Hs.15106, Hs.334808, Hs.140945 together with decreased expression of CD9 antigen (Hs.1244), nuclear receptor subfamily 3, group C, member 1 (Hs.75772) and genes Hs.79741*AA830742, Hs.79742*N24822, Hs.159556, Hs.79123.
AML patients of the learning set classified with predictive values of 100.0% and 88.6% for 5 and 2 year non-survival together with 15.1% and 38.9% for 5 and 2 year survival. The results are similar for the classification of unknown test patients with 100.0% and 79.6% for 5 and 2 year non-survival and 26.9% for 2 year survival. No 5 year survivors were available amongst the test set patients. A data pattern of increased patient age, leukemic cell counts, percentage of CD2, CD4, CD13, CD36 and CD45 positive cells was indicative of 5 year non-survival while 2 year non-survival was characterized by increased patient age, percentage of CD4, CD7, CD11b, CD24, CD45, TH126 and HLA-DR positive cells at decreased percentage of CD1, CD65, CD95 and TC25 positive cells. Data columns with less than 10% of available values remained excluded from the analysis such as LDH, FLT3, LEUK, CD1, CD3, cytoplasmatic CD3, CD41, CD42, CD56, CD58, CD64, CD95 and CD117

in the 5 year survival classification and LDH, LEUK, CD56 in the 2 year survival classification

Conclusion: Classification of multigene expression profiles permits the pretherapeutic identification of high risk non-survivor diffuse large B-cell lymphoma patients for the envisaged chemotherapy. The prediction for survival, in contrast, is unreliable with the available data. Extension of the 12 gene discriminatory data pattern into adjacent molecular pathways may increase the predictivity levels and provide insight into molecular mechanisms of particularly aggressive malignancies. High risk AML patients for 2 or 5 year non-survival can be reliably identified prior to therapy from clinical and malignant immunophenotype parameters while cytogenetic parameters were not selected for the individualized risk assessment.