Drug screening in patient derived xenografts from acute myeloic leukemia and non-Hodgkins lymphoma shows correlation with chemotherapy resistance in patients

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Non-Hodgkin-Lymphomas (NHL) and acute myeloid leukemias (AML) initially respond to chemo- or biological therapy, however some develop resistance becoming aggressively growing tumors. The purpose of our study was the establishment of new PDX models from patients with lymphomas and AML, confirmation of the therapy resistance phenotype, and search for molecular biomarkers.

NHL-PDX were generated from samples of the peripheral blood, lymph node extirpations or fine needle biopsies. From 76 patient samples, we successfully established 13 subcutaneously growing NHL-PDX from B-cell type and 3 from the T-cell type on immune-deficient mice (NOG/NMRI nu/nu mice). Established PDX models from NHL-patients were treated with standard-of-care (SoC) drugs such as cyclophosphamide, vincristine, doxorubicin and rituximab as well as drugs for the second line treatment such as gemcitabine or etoposide.

AML-PDX were derived from bone marrow aspirates or peripheral blood samples, obtained from primary or relapsed AML patients. Purified leukemia cells were transplanted either intravenously (i.v.) and/or subcutaneously (s.c.) into immune-deficient mice. The mice developed a systemic AML, which was monitored by regular flow cytometric analysis of blood samples. Mice were sacrificed when signs of disease were obvious and single cell suspensions of spleens (i.v.) or tumor fragments (s.c.) were transferred to new recipient mice.

Results from the drug screening revealed a correlation of the PDX model response and treatment resistance in patients. Gene expression as well as mutations were analyzed in the PDX of lymphomas and AML within the first in vivo passages. Summarizing, two panels of new PDX models from primary and aggressive NHL’s and AML’s have been established. Different mutations were found in the PDX tumors. Similar to the patients, those PDX models showed different sensitivity to SoC treatment. We established a new systemic AML PDX by i.v.-inoculation. Tracking of human leukemia cells in the blood from the mice allows early evaluation of treatment effects. These new PDX panels of extensively characterized

Summary:

NHL and AML subtypes provide an exceptional platform for the identification and validation of new targets and biomarkers, screening of new compounds and combinations, and for translational as well as personalized oncology research.