

Optimizing genetic diagnostics in hematological malignancies - improving methods to increase cure rates

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All hematological malignancies are characterized by considerable clinical heterogeneity. The diverse entities can be subdivided into a variety of prognosis-defining subtypes on the basis of cytogenetic aberrations and molecular mutations. To adapt the intensity of treatment to the individual risk profile of the patient, an exact classification of the subtypes on the basis of genetic markers is essential. Therefore, a combination of diverse techniques is important to obtain comprehensive characterization. In routine diagnostics classical chromosome banding analyses, fluorescence in situ hybridization, RT-PCR and sequencing are performed at diagnosis of hematological malignancies. Dependent on the disease the clinical impact of different methods vary. Chromosome banding analysis is a standard method for the genetic characterization for acute leukemias, CML and myelodysplastic syndromes accompanied by FISH in certain settings. FISH is the method of choice for the genetic characterization i.e. in multiple myeloma as chromosome banding analysis is hampered in this disease due to low in vitro proliferation. Further, interphase FISH is essential in case of the necessity of rapid confirmation of diagnosis as needed in acute promyelocytic leukemia with the t(15;17)/*PML-RARA* rearrangement where therapy with all-trans retinoic acid (ATRA) should be immediately started. In a variety of hematological diseases mutation analysis is essential to establish the diagnosis, i.e. the detection of a *JAK2* mutation in myeloproliferative neoplasms. In addition, mutation analysis provides important prognostic information, i.e. AML with mutated *NPM1* and without *FLT3-ITD* is one of the most favourable AML subtypes which is not scheduled for stem cell transplantation. Quantitative RT-PCR is the method of choice to monitor minimal residual disease during and after treatment. The "WHO classification of tumours of haematopoietic and lymphoma tissues" requires genetic analysis in the majority of diseases for correct assignment to distinct entities. In addition to karyotype assessed by chromosome banding analysis and mutation status provided by molecular techniques also gene expression analysis is mentioned in order to improve diagnostics in the future. The impact of novel techniques such as genomic arrays and next generation sequencing for diagnostics is currently evaluated. The state of the art diagnostic work up for the most common hematological diseases will be presented. In addition, the potential of new technologies to improve characterization of hematological malignancies and therewith selection of best therapeutic options will be discussed.