## TRANSFORMATION – MODALITY TO EVOLVE IN HEMATOLOGICAL NEOPLASMS

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The ability of cancer to evolve and adapt is a principal challenge to therapy in general, and to the paradigm of targeted therapy in particular.

- In aplastic anemia (AA), immunosuppressive therapy (IST) induces remissions in 50%-70% of patients. Apart from relapse and refractoriness to IST, evolution of clonal diseases, including paroxysmal nocturnal hemoglobinuria and myelodysplastic syndrome (MDS), are the most serious long-term complications. Evolution of MDS occurs either early or late in the course of the disease and constitute a strong argument for definitive therapy with BM transplantation if possible.
- Myelodysplastic syndromes (MDS), one of the most prevalent hematological disorders, constitute a heterogeneous class of stem cell malignancies, characterized by ineffective hematopoiesis in one or more bone marrow (BM) lineages. About one-third of patients with MDS progress to secondary acute myeloid leukemia (sAML). The prognosis of patients who undergo transformation from MDS into sAML is generally grave; most patients are resistant to currently available treatment options and the long-term survival rate among treated patients is <10%.
- Myeloproliferative neoplasms (MPNs) are clonal hematological diseases in which cells of the myeloerythroid lineage are overproduced and patients are predisposed to leukemic transformation. Hematopoietic stem cells (HSCs) are the suspected disease initiating cells and these cells must acquire a clonal advantage relative to non-mutant HSCs in order to perpetuate disease.

- Acute myeloid leukaemia (AML) is an aggressive malignancy characterised by a block in myeloid differentiation and uncontrolled proliferation of abnormal myeloid progenitors that accumulate in the bone marrow and blood. Some cases develop from other haematopoietic disorders or follow genotoxic therapy for unrelated malignancies. AML represents an excellent model for understanding the principles of cancer evolution
- Richter syndrome (RS) is the development of secondary aggressive lymphoma in the setting of underlying chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Most frequently CLL transforms into diffuse large B-cell lymphoma (DLBCL) (90%) and rarely (10%) into Hodgkin lymphoma, termed Hodgkin variant of Richter syndrome (HvRS). There are described two biologically different conditions: CLL transformation to a clonally related DLBCL, that accounts for the majority of cases; development of a DLBCL unrelated to the CLL clone. RS is generally characterized by an aggressive clinical course and poor prognosis.

This ability to evolve is fueled by the co-existence of multiple, genetically heterogeneous subpopulations within the cancer cell population. Increasing evidence has supported the idea that these subpopulations are selected in a Darwinian fashion (Nowell, 1976), by which the genetic landscape of the tumor is continuously reshaped. Recent studies reveal the complex evolutionary trajectories occurring across individual hematological malignancies. They also suggest that while clonal evolution may contribute to resistance to therapy, treatment may also hasten the evolutionary process. New insights into this process challenge us to understand the impact of treatment on clonal evolution, and inspire the development of novel prognostic and therapeutic strategies. This presentation try to summarise the new insights in this process of transformation.