ACUTE MYELOID LEUKEMIA (AML). PATHOGENETIC, DIAGNOSTIC AND THERAPEUTIC ASPECTS.

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Acute myeloid leukemia (LAM) defines a heterogeneous group of clonal hematopoietic stem cell disorders, characterized by abnormal proliferation/accumulation of immature (blastic) myeloid cells and a bone marrow failure syndrome resulting in anemia, hemorrhage and infections. AML heterogeneicity is illustrated in the various classifications used over time: in the WHO 2008 classification, the current „golden standard" approximately 30 morphologically, immuno-phenotipically, cytogenetically and molecularly defined entities are described. Currently, new AML subtypes, defined mainly from a molecular point of view are on the „waiting list" of the future WHO classification. This diversity reflects in fact the multitude of pathogenetic mechanisms that may have as a result the AML phenotype.

Several categories of genetic mutations play a role in AML pathogenesis: mutations affecting kinase genes (FLT3, Ras, Kit, TEL-PDGFRB, JAK2), mutations involving transcription factors (RUNX1, RARA, GATA-1, GATA-2), mutations involving epigenetic regulators (MLL, IDH, DNMT, TET2), mutations involving tumor suppressor genes (NPM1, TR53). Novel mutations have recently been described (MN1, GFI1) in AML cases, their role being still unclear. Moreover cooperation among such mutations in individual patients widens significantly the spectrum of AML subentities.

However, so far the progress in understanding AML biology had a limited impact in „intelligent" treatment strategy design. In most patients, the treatment still consists of antracycline/cytarabine combinations, followed ideally by allogeneic stem cell transplantation. The incorporation of novel „targeted" agents, such as anti-CD33 antibodies (gemtuzumab-ozogamycin), kinase inhibitors (midostaurin, dasatinib, tipifarnib), DNMT inhibitors (azacitidine, decitabine), HDAC inhibitors, did not yield spectacular results. Currently, several clinical trials are trying to establish the role of these new agents in certain AML subentities. Acute promyelocytic leukemia (APL) still remains the AML subtype with the best prognosis; current APL trials try to define the place of arsenic trioxide (either as „salvage" or as first line therapy).

Stem cell allo-transplantation remains the most effective treatment in intermediate and high-risk AML (in fact the majority of patients); however, its use is still restrained by patient age, a limited pool of donors, high costs and relatively high procedure-related mortality and morbidity.

In conclusion, in recent years spectacular progress has been achieved in understanding AML molecular pathogenesis. However, these scientific achievements did not lead yet to a significant improvement of the generally bleak prognosis of the majority of AML patients.