E6. **MANAGEMENT OF ACUTE PROMYELOCYTIC LEUKEMIA IN 2013.**

***Adriana Coliţă*[1], *Andrei Coliţă*[2], *Daniel Coriu*[1]**

[1] Center of the Hematology and Bone Marrow Transplantation of Fundeni Clinical Institute, Bucharest, Romania

[2] Clinic of Hematology, Coltea Clinical Hospital, Bucharest, Romania

Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia characterized by the morphology of leukemic blasts (abnormal promyelocytes), a life-threatening coagulopathy combining disseminated intravascular coagulation, fibrinolysis and fibrinogenolysis, specific reciprocal translocation t(15;17) fusing the promyelocytic leukemia gene (PML) to the retinoic acid receptor alfa (RAR), specific sensitivity to the differentiating effect of all-trans retinoic acid (ATRA) and the proapoptotic effect of arsenic trioxid (ATO). The introduction of ATRA and, more recently, ATO into the therapy of APL has revolutionized the management and outcome of this disease. The treatment strategies using this agents in combination with chemotherapy (CT) have provided excellent therapeutic results: high CR rates (90-94%) and high 5 year DFS rates (> 74%). Once a diagnosis of APL is suspected upon morphologic criteria the disease should be managed as a medical emergency that requires the following rapid and simultaneous actions: a) start treatment with ATRA without waiting for genetic confirmation of diagnosis; ATRA is known to rapidly ameliorate the coagulopathy; b) initiate supportive measures to conteract the coagulopathy and decrease the risk of fatal hemorrhage. Coagulopathy should be treated rapidly with fresh frozen plasma, fibrinogen or cryoprecipitate and platelet transfusions to maintain fibrinogen concentration above 100-150 mg/dL and platelet count above 30-50 x 10^9/L, which should be monitored at least once a day. This measures should be more agresive in patients with higher hemorrhagic risk (older patients, patients with hyperleukocytosis, patients with increased level of creatinine); c) confirm diagnosis in bone marrow at the genetic level. Demonstration of the t(15;17) or its counterpart, the PML/RAR hybride gene by conventional karyotyping, FISH or RT-PCR is mandatory because the efficacy of differentiation treatment based on retinoids is strictly dependent on the presence of the PML/RAR fusion in leukemia cells. RT-PCR is the "gold standard" approach for confirming a diagnostic of APL. RT-PCR allows definition of the type of PML-RAR isoform and the target for monitoring MRD. Morphologic diagnosis in bone marrow, although highly predictive of the specific genetic lesion in hypergranular tipical cases is considered insufficient. A morphological suspicion of PML-RAR positive APL can be remforced by the study of the characteristic immunophenotypic features of blast cells by multiparameter flow cytometry. Once the diagnosis has been confirmed at the genetic level, targeted induction therapy should be promptly started with ATRA combined with anthracycline based-chemotherapy. 20% patients with APL treated with ATRA (and ATO) can experience the APL differentiation syndrome and treatment with dexamethasone should be promptly started at very earliest sign or symptom. Distinct from AML, early morphologic evaluation of bone marrow has no value in APL. Morphologic features in bone marrow during differentiation therapy can be misleading and some-times erroneously interpreted as resistence. This features showing delayed maturation or persistance of atypical promyelocytes are occasionally detectable several weeks after the start of treatment (up to 50 days). An accurate assessment of RT-PCR status of the end of consolidation is crucial because patients who show residual PML/ RAR transcripts at this time point are candidate for further intensification, whereas those who test PCR negative would proceed to receive maintenance. The small fraction of patients who test PCR-pozitiv for the PML/RAR hybride gene at the end of consolidation (molecular persistance) have a dismal prognosis and should receive additional therapy aimed at obtaining molecular remission including ATO, novel agent auto or allogeneic hematopoietic stem cell transplantation (HSCT). For patients with hyperleucocytosis is reasonable to recomand a stringent monitoring, at least every 2 months in the early postconsolidation period and there after every 3 months for two years. The APL status has evolved from highly fatal to highly curable.