MANAGEMENT OF ACUTE PROMYELOCYTIC LEUKEMIA: "THE GOLDEN HOUR"

Gabriel Ghiaur[1], Alexandra Ghiaur[2]
1 – Adult Leukemia Program, Division of Hematological Malignancies, Johns Hopkins, Baltimore, USA
2 – Division of Hematology, Fundeni Clinical Institute, Bucharest, Romania

Management of acute promyelocytic leukemia (APL) is the perfect example for how translational research changed clinical practice in hematology-oncology. Over the last three decades, APL transformed from one of the worst diagnosis in hematologic malignancies, a nightmare for patients and physicians alike to a highly curable disease, a gratifying experience for leukemia doctors. In 1977, Rowley et al. identified a unique genetic abnormality, "t(15;17) (q22?;q21)" as the hallmark of APL blasts. In the 1980's, inspired by traditional Chinese remedies, Huang et al. determined that pharmacological levels of retinoids can terminally differentiate APL blasts with emergence of neutrophils. The subsequent integration of all-trans retinoic acid (ATRA) into APL treatment paradigms became the first targeted therapy in hematology, twenty years before the use of Imatinib in chronic myeloid leukemia. Unfortunately, single agent ATRA induces "remission without cure" in APL and these studies first proposed the existence of "minimal residual disease" (MRD) as malignant cells that are present even though the patient is in morphological remission. Since then, MRD became a term routinely used in hematological malignancies and oncology in general. The mechanism by which MRD persists in APL patients treated with single agent ATRA remains an area of active research. One hypothesis, proposed by our group this year suggests that the bone marrow microenvironment metabolize ATRA and thus, protects some APL cells. If so, this may explain why liposomal ATRA can single handedly cure some APL patients. Nevertheless, over the last two decades, the addition of arsenic trioxide (ATO) to ATRA was able to eliminate MRD, decrease relapse in APL and improved cure rates even without cytotoxic chemotherapy.

From a clinical standpoint, current challenges in APL gravitate around rapid diagnosis and initiation of ATRA, management of coagulopathy and differentiation syndrome. To this end, we will use two clinical vignettes to showcase our approach at Johns Hopkins towards patients with this disease. Briefly, any patient suspect of APL has a peripheral blood smear reviewed by a hematologist within 30 minutes. Presence of circulating malignant promyelocytes, sometimes hypogranular, results in initiation of ATRA therapy. Peripheral blood flow cytometry is used to further support a diagnosis of APL based on a combination of cell surface markers (CD33 bright, HLA-DR negative, CD34 negative), though various staining patterns could be identified more so if Flt3 mutations are present. A hematopathologist together with a hematologist review these results within hours from admission. In most cases, the diagnosis is confirmed by FISH for t(15;17) within 36-48h and later on by classical karyotype and RT-PCR for PML-RARα.

The initial management of patients with APL is geared towards treating infectious complications and diffuse intravascular coagulation (DIC). Regarding management of DIC, in addition to initiation of ATRA therapy which should address the underlying pathophysiology of uncontrolled fibrinolysis, supportive measures include transfusion of platelets and fibrinogen rich products (preferable cryofibrinogen). There are currently no clear indications for the use of unfractionated heparin, tranexamic acid or rhThrombomodulin, though these products will be discussed with potential risks and benefits.

Regarding APL-directed therapy, based on Lo Coco et al. 2013, patients with WBC over 10000/mm3 at presentation are treated with ATO+ATRA while those with more than 10000/mm3 are treated with ATRA and Idarubicin based on Gore S et al. Even though this classification is rather arbitrary, the lack of cytotoxic chemotherapy in ATO+ATRA regimen does bring some interesting challenges (i.e. hyperleucocytosis and differentiation syndrome) that will be discussed. Nevertheless, in spite of potential complications, these patients have lower risk of severe infections and thus, decreased hospitalization and better outcomes.

Finally, since the cure rate in APL reaches over 90% in some cases, it remains unclear the role of monitoring MRD during consolidation. Patients with relapsed APL, if they were not previously treated with ATO will receive ATRA+ATO. If refractory to ATO based therapy, they can be treated with either cytotoxic therapy followed by autologous/allogeneic BMT or by anti-CD33 (Gemtuzumab). While not approved by FDA in US, Tamibarotene is approved in Japan and is available for compassionate use or as part of a clinical trial. Lastly, based on our most recent laboratory data, a clinical trial using a novel synthetic retinoid for treatment of relapsed refractory APL and non-APL AML is currently being developed at Johns Hopkins.