Crossroads in Acute Leukemia: Mixed Lineage APL – ETO Acute Myeloid Leukemia

Muhammad Nadeem, Nayab Khan
Department of Oncology, Combined Military Hospital, Rawalpindi; Resident Medical Oncology, Combined Military Hospital, Rawalpindi

Introduction
Acute Myeloid Leukemia (AML) is one of the two major forms of acute leukemia. It accounts for about 25% of all adult leukemias diagnosed in the west. It is primarily a disease of late adulthood with mean age of diagnosis 65 years. Diagnosis of AML in children and young adults is fairly uncommon comprising only 15–20% of all acute leukemia in children less than 15 years of age. AML has been classified using the French-American-British (FAB) classification into various subtypes (M1-M6) depending upon certain morphological characteristics. This has further been elaborated by the WHO based on the distinct cellular appearance, immunophenotypic profile and associated cytogenetic mutations. Not only do these help in identification of AML type, but also serve as a guide to treatment responsiveness and prognosis. However, approximately 45% of AML patients have normal cytogenetics and are the most diverse group with regards to treatment response and prognosis. Within this sub group other gene mutations have been described that confer better or worse prognosis. Treatment options traditionally consist of the standard ‘3+7’ regimen for AML other than M3 and protocols including oral all trans-retinoic acid (ATRA) for AML-M3. We report a case of 38 years old male who was diagnosed as a case of mixed lineage APL – ETO acute myeloid leukemia and was managed merging the treatment strategies for FAB AML - M2 and FAB AML - M3. He achieved complete hematological and molecular remission.

Case Report
A 38-year-old male patient, was admitted to Combined Military Hospital (CMH) Lahore in Nov.2014 with 01-week history of high grade fever and easy fatigability. At presentation he was pale with a temperature of 102°F, while the rest of general physical and systemic examination was normal. His Complete Blood Picture revealed Hb 7.1g/dL, TLC 49.9x10^9/L and Platelets 18x10^9/L. Peripheral blood film showed 80% blasts along with 02% promyelocytes. All the other investigations were within normal limits, including coagulation profile. Bone Marrow Biopsy was done on 3rd day of admission showing Acute Myeloid Leukemia with 40% blasts and few Auer rods. Immunophenotyping (IPT) study was suggestive of AML-M2 (CD45++, CD 13++, CD 11b++, CD 11c+, CD17++, HLA DR++, MPO++). He received parenteral broad spectrum antibiotics and 03 units of red cell concentrates were transfused. Repeat bone marrow examination for IPT, molecular markers and cytogenetic studies was done at CMH Rawalpindi. The second bone marrow report was suggestive of Acute Promyelocytic Leukemia (APL) with IPT of this sample also suggestive of the same. The PCR for AML gene markers was positive for AML1-ETO translocation while PCR for PML-RARα was also weak positive. His PT/PTTK, plasma fibrinogen and d-dimers were all within normal limits. With a provisional diagnosis of acute promyelocytic leukemia, he was started on chemotherapy AIDA according to APL-PETHEMA protocol. Review of both his bone marrow samples and molecular studies was requested. The results corroborated earlier findings and a final diagnosis of mixed lineage APL/AML-ETO leukemia was made. Post Induction bone marrow revealed that the patient was not in hematological remission with 15% blasts and abnormal promyelocytes. PCR for PML-RARα was still weak positive. He received first cycle of consolidation chemotherapy according to APL-PETHEMA. Post first consolidation bone marrow biopsy revealed the patient had achieved hematological remission with <5% blasts in bone marrow. However, PCR for PML-RARα was still weak positive. The patient was discussed in hematology oncology meeting and keeping in view the mixed nature of his leukemia, second consolidation chemotherapy was administered with high dose cytarabine (HiDAC) with addition of oral all trans-retinoic acid (ATRA) at the dose of 45mg/m². Bone marrow aspiration after second chemotherapy (Feb.2015) was showing hematological remission with <1% blasts and negative PCR for PML-
RARα. The patient received third consolidation with same HiDAC and ATRA as before. Post third consolidation his bone marrow examination confirmed remission with < 1% blasts, no abnormal promyelocytes and negative PCR for PML-RARα. Considering the high risk of relapse and poor prognosis, the option of allogeneic bone marrow transplant was discussed with the patient which he declined. Currently he is on maintenance chemotherapy as per APL-PETHEMA protocol and is post 5th month. We plan to complete 24 months maintenance.

**Discussion**

Despite attempts to define the boundaries of classification based on blast percentage, there exist ambiguities and grey areas whereby the blasts become harder to place into a certain distinctive category. This can be a mixture of both myeloid and lymphoid blasts or mixture of two different subsets or lineage of blasts within the same category (Myeloid or Lymphoid). The European Group for the Immunological Characterization of Acute Leukemias (EGIL) has proposed a scoring system based upon CD markers in an effort to aid in distinguishing biphenotypic acute leukaemia (BAL) from various leukaemia subtypes. The new WHO classification of hematologic tumours has adopted the EGIL criteria for BAL and introduced a new group of acute leukaemia termed 'acute leukaemia of ambiguous lineage'. In addition to BAL in which a single cell population expresses both myeloid and lymphoid differentiation markers, this new group of leukemias also comprises cases that present with two separate blast populations (acute bilinealleukemia, aBLL). In general, BAL accounts for less than 5% of all acute leukaemia cases, whereas aBLL is a rare disease constituting 1%-2% of acute leukaemia cases that contains B- or T-lymphoid blasts along with myeloid blasts. In addition to these subtypes which co-exist, cases have been reported where acute myeloid leukaemia has evolved with time into other myeloid or lymphoid phenotypes. A case reported by Cioli and colleagues described a patient with acute myeloid leukaemia at diagnosis with a small subset of lymphoid lineage blasts had a switch to pure lymphoid leukemia at first relapse. Limited number of data has been published of co-existing FAB AML-M2 and AML-M3 (promyelocytic leukemia) and not much is known about this entity and the most appropriate management strategy. It has also been suggested that PML-RARα is expressed by limited population of blasts in AML other than M3 and its use in routine molecular screening. The study conducted by MRC adult leukemia working party found expression of PML-RARα in patients diagnosed as AML-M1 and AML-M2 respectively but it was very uncommon thus un-warranting routine testing. Braham and colleagues reported the identification of PML-RARα transcripts in a patient previously diagnosed as AML-M1 who was treated with standard 3+7 chemotherapy regimen for acute myeloid leukemia and achieved hematological and molecular remission. Few cases have been reported in literature of simultaneous PML-RARα and AML1/ETO expression in a patient in whom only AML1/ETO gene expression (FAB AML-M2 morphology) was detectable on relapse after chemotherapy. No standard treatment protocol has been described in such patients with mixed leukaemias. In our patient, we employed the chemotherapy protocol APL-PETHEMA for acute promyelocytic leukemia which was the provisional diagnosis at the time of commencement of therapy. Urgent initiation of chemotherapy was also necessary as acute promyelocytic leukemia can quickly be complicated by life threatening coagulopathy. Based on leukocytosis and thrombocytopenia, the patient was classified as high risk according to the risk stratification criteria proposed by Sanz et al. Although he did not achieve complete remission after induction chemotherapy but there was a significant reduction in the percentage of marrow blasts and hence first consolidation with ATRA and anthracycline chemotherapy was administered which led to hematological remission. Second and third consolidation chemotherapy courses comprised of high dose cytarabine and oral ATRA. Although the potential benefit of the addition of cytarabine has been suggested in previous studies, the specific use of this agent for high-risk patients was mainly supported by a joint study of the PETHEMA and the European APL groups. The authors have suggested a benefit in terms of reduction of relapse risk with the use of cytarabine in consolidation in patients with high-risk disease. The patient is currently on maintenance chemotherapy as per APL-PETHEMA protocol. There is only a limited amount of data mostly in the form of published case reports on the prognosis of such patients over time and whether allogeneic bone marrow transplant in first remission is a suitable option. However, most of the patients described either did not achieve a remission or relapsed shortly after or during consolidation therapy with fatal outcomes. It has been
postulated that the two different blast populations overlap at key points in their multiplication cycles, suppressing one with appropriate chemotherapy might not have an affect as alternate signalling pathways will continue the abnormal cell proliferation. Standard treatment targeting known pathways may be inadequate for full disease control making it harder to achieve and sustain durable remission. After decades of clinical experience, the treatment strategies for acute myeloid leukaemia are still evolving to prolong sustained remission. On the crossroads of such management one often finds himself on the horns of dilemma where managing hybrid and mixed lineages becomes still more difficult.

References