Case Report

Acute Promyelocytic Leukemia with Early CNS Relapse

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Introduction

Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia (AML) characterized by reciprocal translocation between long arms of chromosome 15 and 17 t(15;17) and presentation with severe coagulopathy which may lead to early death. APL accounts for 10-15% cases of AML. The introduction of all-trans retinoic acid (ATRA) has revolutionized the treatment of APL by almost doubling the cure rate.1 Central nervous system (CNS) involvement can occur at the time of relapse. The incidence of CNS relapse in APL ranges from 0.6-2% and is seen most commonly in patients presenting with total leucocyte count (TLC) count greater than 10x10^9/L i.e high risk patients. The 5 year cumulative incidence of CNS relapse in these high risk patients is 5.5% and median time to relapse is 16 months.2 The present case is of young man who while receiving maintenance therapy developed CNS relapse followed closely by molecular relapse.

Key Words: Acute promyelocytic leukemia, CNS relapse

Case Report

A 31 year old male presented at Combined Military Hospital (CMH), Rawalpindi in April 2013 with one week history of fever and bleeding from nose, gums and haematuria. On examination the patient exhibited haemodynamic stability and normothermia. He had few purpuric spots on anterior abdominal wall. Rest of the systemic examination was unremarkable. Laboratory work up revealed deranged coagulation profile and blood CP showed TLC count 26.6x10^9/L, Hb 12 g/dl and Platelet count 17x10^9/L. Bone marrow examination showed 90 % blasts with abnormal promyelocytes and was diagnosed as AML-M3 (Acute promyelocytic leukemia). He was classified as high risk due to high TLC and low platelet count according to Sanz criteria.3 Patient was commenced on APL PETHEMA 2005 protocol along with prophylaxis of differentiation syndrome. His treatment was complicated by lower respiratory tract infection and ATRA was temporarily withheld for 6 days due to worsening of respiratory symptoms. Bone marrow recovery was seen at day 26 and post induction bone marrow examination revealed a moderately hypocellular marrow with less than 1% blasts. At this time cytogenetics report revealed normal male karyotype with no structural or numerical abnormality. PCR for PML-RARα was negative after induction phase. Patient then proceeded on to receive 3 cycles of consolidation chemotherapy at 3 weekly intervals. PCR for PML-RARα done from bone marrow after consolidation in September 2013 was negative and so he was started on oral maintenance therapy. In February 2014 he presented in emergency with intense headache and vomiting. There were no clinical signs of meningeal irritation and CT scan brain was normal. CSF analysis showed cell count 100/ul with few blast cells. Repeat bone marrow examination revealed less than 2% blasts and positive PCR for PML-RARα. He was given thrice weekly intrathecal chemotherapy with Methotrexate, Cytarabine and Hydrocortisone till CSF analysis was normal. He also received whole brain radiotherapy 2GY/Fraction to total dose of 24 GY. As his PCR for PML-RARα was positive so he was initiated on second line induction chemotherapy with Arsenic trioxide (ATO) for 30 days. Post induction bone marrow exhibited 2% blast cells, abnormal promyelocytes and positive PCR for PML-RARα. He had till date received 3 cycles of ATO consolidation as per protocol mentioned by Lazo and colleagues.4 Response assessment done after consolidation by repeating bone marrow showed haematological remission, negative PCR for PML-RARα and a normal CSF. His last cytogenetics report is still showing normal male karyotype with no numerical or structural abnormality. Further treatment is planned as maintenance therapy( APL PETHEMA 2005 protocol) with addition of three monthly intrathecal therapy.

Discussion

Despite the dramatic improvement in treatment strategy of patients with APL, CNS relapses are seen in patients presenting with high TLC count and are
almost unvaryingly associated with molecular or hematologic relapse. Risk stratified treatment of APL is being adapted as to reduce treatment related morbidity and mortality and to improve outcome particularly in those at highest risk of relapse. The PETHEMA group conducted a study in which high risk patients defined as those having TLC count greater than 10x10⁹/L received cytarabine combined with ATRA and Idarubicin in first and third consolidation courses. Although there were no differences in OS and PFS with the addition of cytarabine in management of high risk patients, the 3 year relapse rate decreased from 26% to 11% thus making this approach a standard treatment for high risk APL. The incidence of CNS relapse in low risk and high risk patients is 1.2% and 5.5% respectively. Various risk factors have been suggested to predict the advent of CNS relapse in APL like age, BCR isoforms, CNS haemorrhage during induction chemotherapy, use of ATRA and development of differentiation syndrome. It has been suggested that the incidence of CNS relapse in APL has increased after the advent of ATRA. ATRA not only upregulates the expression of several adhesion molecules including CD11b, CD13 but also increases the secretion of Interleukin 1 and enhances the endothelial expression of VCAM 1 and ICAM 1, all predisposing to CNS relapse. Another probable elucidation for increase in incidence of CNS relapse is effective treatment regimens leading to prolonged survival. The most consistent risk factor associated with CNS relapse remains the high total leucocyte count at first presentation. Our patient was classified as high risk and was treated accordingly. Despite achieving complete remission he relapsed after receiving 5 months of oral maintenance. Routine use of CNS prophylaxis with Intrathecal chemotherapy or high dose chemotherapy in management of high risk patients with APL remains vague and needs to be addressed further considering increased incidence of CNS relapse in high risk patients.

The prognosis of patients with CNS relapse in APL is still uncertain because of the paucity of the disease. According to GIMEMA study the outcome of patients with CNS relapse was similar to those with isolated hematologic relapse. This was contrary to study led by PETHEMA and European APL group who observed poor outcome in patients with CNS relapse. The optimal management of patients with CNS relapse has not been discriminatingly evaluated. Arsenic trioxide is considered to be the standard of care for relapsed acute promyelocytic leukemia. Half of the patients can presumably be cured with ATO based salvage therapy. The three years overall survival for patients with extramedullary relapse is significantly better compared to patients with haematologic and molecular relapse (90% vs. 69% and 66%). Our patient developed both CNS and molecular relapse and was treated with Intrathecal chemotherapy, cranial radiation and ATO. He tolerated and responded well to treatment and achieved complete molecular remission after consolidation with ATO. Whether development of early relapse followed by complete response effects relapse free survival or overall survival needs further follow up.

References