CNS relapse in a low risk acute promyelocytic leukemia patient treated with ATRA-based regimen: is there a role for prophylactic CNS therapy in acute promyelocytic leukemia?

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Abstract Though the incidence of CNS relapse in acute promyelocytic leukemia (AML-M3 FAB classification) has increased following the advent of all-trans retinoic acid (ATRA), still CNS relapse accounts for only 2–3% of all relapses in AML-M3 treated with standard ATRA plus chemotherapy regimen. We report a case of low risk AML-M3 treated with standard therapy, developing CNS relapse while on maintenance therapy with ATRA + 6-mercaptopurine (6-MP) + methotrexate (MTX).

Keywords Acute promyelocytic leukemia · CNS relapse · Prophylactic CNS therapy · All-trans retinoic acid

Introduction

Acute promyelocytic leukemia (AML-M3 FAB classification) has the best prognosis among the acute myeloid leukemias with a relapse free survival at 27 months of 100% in low risk, 90% in intermediate risk and 75% in high risk cases with standard all-trans retinoic acid (ATRA) plus anthracycline induction followed by anthracycline-based consolidation and ATRA + 6-mercaptopurine (6-MP) + methotrexate (MTX) maintenance [1]. Though there is an increase in cases of relapse in the CNS after the introduction of ATRA, still CNS relapse is very rare in AML-M3 [2]. Relapse in the CNS accounts for only 2–3% of all relapses, majority of it occurring in high risk cases. Hence prophylactic CNS therapy is not a standard in the treatment of AML-M3. The present case is the first report of a low risk AML-M3 patient treated with ATRA plus daunorubicin induction followed by 4 cycles of anthracycline-based consolidation and maintenance therapy with ATRA + 6-MP + MTX, relapsing in the CNS while on maintenance treatment.

Case report

A 37-year-old male presented to us in October 2007 with history of uncontrollable bleeding from tooth extraction site. On evaluation, Hb was 105 g/l, WBC count $2.5 \times 10^9/l$ with 93% atypical promyelocytes and platelet count $48 \times 10^9/l$. FDP was elevated 400 ng/ml. Bone marrow aspirate was hypercellular with 92% atypical promyelocytes. RT-PCR for PML-RAR- α short isoform done from the bone marrow was positive (20.61%). His disease was categorized into low risk group according to Sanz criteria [1]. He was treated with ATRA 45 mg/m² till hematological remission plus daunorubicin 45 mg/m² for 3 days. He achieved

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complete hematological remission after 47 days, following which he was given two more courses of daunorubicin followed by 2 courses of mitoxantrone. RT-PCR for PML-RAR- α done from the marrow after consolidation in February 2008 was negative and was started on maintenance with ATRA + 6-MP + MTX. A repeat RT-PCR for PML-RAR- α done in May 2008 was also negative.

In December 2008 he developed intense headache with occasional vomiting. MRI of the brain was normal. Lumbar puncture showed 587/ μ l atypical promyelocytes. His blood counts were normal, bone marrow morphology was normal, but RT-PCR for PML-RAR- α was positive (2.5%). He was given twice weekly intrathecal therapy with MTX and cytarabine till CSF was negative for promyelocytes and at the time of writing this report he is receiving weekly intrathecal therapy and is being planned for cranial irradiation. As his RT-PCR for PML-RAR- α is positive he is started on arsenic trioxide.

Fig. 1 Promyelocyte in CSF of the patient at the time of CNS relapse in December 2008. Large hypergranular cell with eccentric nucleus. Leishman stain-400 $\times$ magnification

CNS is a rare site for relapse in AML-M3. After the advent of ATRA, more cases of CNS relapse have occurred; still CNS relapse in low risk (as WBC count at presentation is $<10 \times 10^9/l$ and platelet count is $>40 \times 10^9/l$) disease is even rarer. Reason for increase in cases of CNS relapse in patients treated with ATRA has been hypothesized to be the upregulation of adhesion molecules on the leukemic cells induced by ATRA which is a differentiating agent [2–4]. Or is it simply a consequence of increased survival of AML-M3 patients after the introduction of ATRA? Our case raises a few important issues in the treatment of this potentially curable disease: 1) Should prophylactic cranial therapy be a routine in the management of AML-M3? 2) Cytarabine is usually reserved for high risk cases. Is intermediate or high dose cytarabine required in all cases of AML-M3 irrespective of the risk category? Finally the dose of daunorubicin used was 45 mg/m². Daunorubicin does not cross the blood brain barrier and hence does not have much role in CNS disease. But our patient had a molecular relapse at the time of CNS relapse. Would a dose of 60 mg/m² or another anthracycline like idarubicin prevented the molecular relapse and probably the CNS disease?

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