

All trans-retinoic acid in the treatment of promyelocytic leukaemia – a case report

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Summary

A six year old Chinese boy with relapsed Acute Promyelocytic Leukaemia (APML) failed to respond to reinduction with Daunorubicin and Cytarabine infusion. He was successfully treated with all trans-Retinoic Acid (45 mg/m²/day) orally. After four weeks of treatment, he was in complete remission. The side effects of all trans-Retinoic Acid were negligible.

Key words: Acute promyelocytic leukaemia, all-trans retinoic acid, differentiation

Introduction

Acute Promyelocytic Leukaemia (APML) is an uncommon type of acute non-lymphocytic leukaemia (ANLL)¹. Treatment of APML is associated with significant mortality and morbidity. Ten to twenty per cent of the patients die early of fatal haemorrhage resulting from coagulopathy and sepsis. An alternative approach to the treatment of APML has centered on the use of differentiating agents to induce remission. Recent therapeutic trials confirm that all-trans retinoic acid is a safe and highly effective agent for inducing complete remission in APML^{2,3,4,5}. We report a child with relapsed APML who failed reinduction with conventional chemotherapy but responded to all trans-retinoic acid.

Case

The patient is a 6 year old Chinese boy who presented with recurrent episodes of epistaxes, fever and pallor of one month's duration. Physical examination did not reveal any abnormality except severe pallor. There was no hepatomegaly, splenomegaly or lymphadenopathy.

Peripheral full blood picture showed a haemoglobin of 5.7g/dl and leucocyte count of 2000/mm³ with 4% blast cells. Bone marrow aspiration examination confirmed a diagnosis of Acute Promyelocytic Leukaemia (FAB M3). Baseline coagulation profile was normal.

Induction chemotherapy consisted of Prednisolone 60mg/m² orally, Cytarabine 100mg/m² intravenous infusion for five days and Daunorubicin 50mg/m² intravenously on Days 1,3 and 5. He received three courses of the above regime at three weekly intervals. During chemotherapy, he developed bleeding diathesis with gastrointestinal haemorrhage and bleeding gums. Investigations showed thrombocytopenia and abnormal coagulation profile and he was treated with transfusions of platelet concentrates and fresh frozen plasma.

A repeat bone marrow aspiration examination showed that he was in remission. The parents refused a bone marrow transplant and he was then given cranioprophylaxis and then put on maintenance chemotherapy with 6 mercaptopurine, 6-Thioguanine and cytarabine.

Eleven months later he developed a bone marrow relapse and reinduction chemotherapy with intravenous Daunorubicin and Cytarabine infusion at three weekly intervals was given for three months but failed to induce remission. He was then started on all-trans retinoic acid (45mg/m²/day) orally. Coagulation profile and liver function tests were closely monitored and remained normal throughout treatment. Side effects consisted of headaches, nausea, vomiting and angular stomatitis. As he tolerated the drug well, his treatment was done on an outpatient basis.

After four weeks of all-trans retinoic acid, the bone marrow aspiration examination showed that he was in remission. All-trans retinoic acid was stopped and consolidation chemotherapy started with Cytarabine, Adriamycin and Vincristine. He has now been in remission for six months and is being planned for a bone marrow transplant.

Discussion

A peculiar feature of APML is the high incidence of DIVC. This has been shown to result from the release of a procoagulant factor by the blast granules. The DIVC is made worse by cytotoxicity during induction chemotherapy, thus pushing mortality rates to as high as 47%.

Retinoids (Vitamin A and its natural and synthetic analogues) are important in the regulation of proliferation and differentiation of epithelial tissues and Breitman⁶ showed that retinoic acid induces differentiation of promyelocytes into mature granulocytes in-vitro.

In 1986, Huang et. al⁴ conducted the first therapeutic trial with twenty-four patients with APML using all trans- retinoic acid. Twenty three patients attained complete remission without any coagulation abnormality and minimal side effects. Similar trials by Castaigne et al¹ in 1988 and Warrell et al⁵ in 1990 achieved complete remission rates of 64% and 82% respectively and again the side effects were minimal.

The exact mechanism of action of retinoic acid is not known. A distinct chromosomal abnormality – 15;17 translocation has been detected in most patients with APML. Gene probing has shown that the breakpoint on chromosome 17 is in the region of the retinoic acid receptor – alpha (RAR- α)⁷. This receptor is involved in the growth and differentiation of promyelocytic cells in-vitro. The expression of abnormal messenger RNA (mRNA) transcripts for RAR- α is markedly decreased or disappears as patients entered into complete remission. Retinoic acid has been shown to be most effective in APML patients with 15;17 translocation. Unfortunately, in our patient, the chromosomal analysis was not done. No cytodifferentiating activity has been described in preliminary clinical studies of other myeloblastic leukaemias that lack the 15;17 translocation^{1,4}.

Apart from being able to induce complete remission in APML, all-trans retinoic acid does not cause or aggravate any coagulation abnormality. The incidence of sepsis is also low and mild. Furthermore, it can be taken orally and the side effects are mild and minimal, mainly dryness of lips and skin, headache, nausea and vomiting, moderate bone or joint pain, mild exfoliation, hypertriglyceridemia and elevated alanine aminotransferase. Rarely, benign intracranial hypertension has been reported.

In conclusion, all trans- retinoic acid (45mg/m²) is recommended as a sole agent for induction of remission in APML.

References

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