HK J Paediatr (new series) 2023;**28**:41-45

Case Report

Sublingual Capsular All-*trans* Retinoic Acid for Induction Treatment of Acute Promyelocytic Leukaemia in a Child

GPY ***Tong***, JKH ***Chiu***, CW ***Luk***, SY ***Ha***

Abstract Oral all-*trans* retinoic acid (ATRA) is an integral part of acute promyelocytic leukaemia (APL) treatment. However, it poses difficulties for patients who cannot tolerate oral medication. We report a child with APL which was complicated by ruptured acute appendicitis and paralytic ileus. As a result, oral ATRA was administered sublingually during induction. Clinical remission was achieved after induction and the patient went on with subsequent chemotherapy with no relapse for more than 3 years from diagnosis. We reviewed the literature about the necessity of ATRA in APL treatment and how sublingual ATRA was used.

Key words *Acute promyelocytic leukaemia; All-trans-retinoic acid*

Introduction

Acute promyelocytic leukaemia (APL) is a rare form of acute myeloid leukaemia (AML), with paediatric annual incidence of only 2-4 in Hong Kong.[1] It is characterised by a balanced reciprocal translocation between chromosomes 15 and 17, resulting in the fusion between the promyelocytic leukaemia (PML) gene on chromosome 15 and retinoic acid receptor-alpha (RARA) gene on chromosome 17.[2]

Department of Paediatrics, Hong Kong Children's Hospital, 1 Shing Cheong Road, Kowloon Bay, Kowloon, Hong Kong SAR, China
GPY **Tong** (唐沛容) *MBBS*
CW **Luk** (陸頌榮) *MBBS*
SY **Ha** (夏修賢) *MBBS*

Department of Paediatrics, Queen Elizabeth Hospital, 30 Gascoigne Road, Kowloon, Hong Kong SAR, China
JKH **Chiu** (趙嘉豪) *MBBS*

Correspondence to: Dr GPY **Tong**
Email: grace.tong@ha.org.hk

Received March 3, 2021

Currently, APL patients are treated with chemotherapy protocols which incorporate the use of oral all-*trans* retinoic acid (ATRA). Other dosage forms of ATRA, e.g. intravenous or per-rectal, are not available. Thus challenges exist for patients with conditions rendering oral administration of the drug impossible, e.g. intestinal obstruction, decreased consciousness, and dysphagia.

Case Presentation

In November 2016, a 12-year-old Chinese girl was admitted for fever, abdominal pain and watery diarrhoea for a week. She had increased skin bruising for a month. Physical examination showed pallor, signs of dehydration (dry lips and oral mucosa) and bruises over bilateral anterior shins. There was no hepatosplenomegaly or lymphadenopathy. Her abdomen was soft and non-distended with mild tenderness over the right side. The first complete blood count showed anaemia (haemoglobin 4.5 g/dL) and thrombocytopenia (platelet count $14x10^9$/L). Total white cell count was $6.6x10^9$/L, with essentially no neutrophils, an absolute lymphocyte count of $0.5x10^9$/L

(7%), but abundant (93%) circulating hypergranular promyelocytes. Rare faggot cells were also seen. Red cells showed mild poikilocytosis with occasional red cell fragments and tear-drop cells. She also had disseminated intravascular coagulopathy (DIC), with an international normalised ratio of 1.56, prolonged prothrombin time to 17.9s, prolonged activated partial thromboplastin time to 45.8s, a normal fibrinogen level of 1.6 g/L and raised d-dimer level of >5000 ng/mL. Peripheral blood Reverse transcription-polymerase chain reaction (RT-PCR) for PML-RARA fusion transcript was positive. Karyotyping showed 46,XX,t(15;17)(q22;q12)[10]. These confirmed the diagnosis of acute promyelocytic leukaemia with PML-RARA translocation complicated by DIC. The patient was sent to paediatric intensive care unit for close monitoring. Supportive care, including broad spectrum antibiotics, packed cells, platelet concentrate and fresh frozen plasma transfusion, were given.

Induction chemotherapy based on the International Consortium for Childhood APL 2001 protocol,[3] consisting of oral ATRA and intravenous idarubicin, was started. As the total white cell count rose to >10x10^9/L before commencement of treatment, the patient was stratified to high risk group. Initially, ATRA 20 mg om and 10 mg pm were to be started, together with intravenous dexamethasone for preventing ATRA syndrome. However, after one dose of oral ATRA 20 mg, her abdominal pain worsened. Computerised tomography of the abdomen and pelvis with contrast showed multiple long segments of dilated small bowel loops, with circumferential mural thickening at the distal and terminal ileum. The overall clinical picture was compatible with acute appendicitis with paralytic ileus. All oral medications, including ATRA, were withheld, while intravenous idarubicin was given according to schedule.

After discussion and literature review, sublingual capsular ATRA was used as an alternative. The capsule was first softened with warm water and then put on the patient's tongue base (Figure 1). ATRA 20 mg om and 10 mg pm were administered sublingually with this method. After 30 minutes of each administration, the capsule would be taken out for visual examination to ensure that the capsule was emptied, with all the content diffused out and absorbed sublingually. Clinical response was noted, with improvement in cell count and clotting profile and reduction in platelet and plasma transfusion requirement after three days of sublingual capsular ATRA.

For her acute appendicitis and paralytic ileus, medical treatment, including intravenous antibiotics, complete bowel rest and nasogastric tube aspiration, was initially given. However, condition did not improve. Eventually open laparotomy was required. Intra-operatively, grossly dilated small bowel loops, post-ileal appendix already being broken off from its base, with surrounding localised abscess with necrotic tissue were noted. Surgical diagnosis of acute appendicitis, with perforation and abscess formation and paralytic ileus of small bowel was made. Histology of the surgical specimen revealed inflammatory cells without leukemic infiltrate. Peritoneal swab, blood and stool cultures remained negative. Chemotherapy, which was sublingual ATRA alone at that time, was withheld since day 15 of induction. Subsequently, it was further withheld due to hyperbilirubinaemia and deranged liver function, which was suspected to be caused by intra-abdominal sepsis. As she recovered from her surgery and her liver function improved, sublingual ATRA was resumed on post-operation day 9 (i.e. day 24 from start of induction), initially at a lower dose of 10 mg daily for four days, and then increased to 10 mg BD till the end of induction (Figure 2), completing a total of 30 days of ATRA administration.

Morphological remission was successfully achieved, as post-induction bone marrow assessment showed absence of promyelocyte and adequate trilineage haematopoiesis. Peripheral blood for RT-PCR for PML-RARA fusion transcript was negative.

Subsequently, consolidation chemotherapy and maintenance chemotherapy were given without significant delay. After three courses of consolidation chemotherapy and two years of maintenance chemotherapy, patient completed treatment in May 2019, i.e. 29 months after

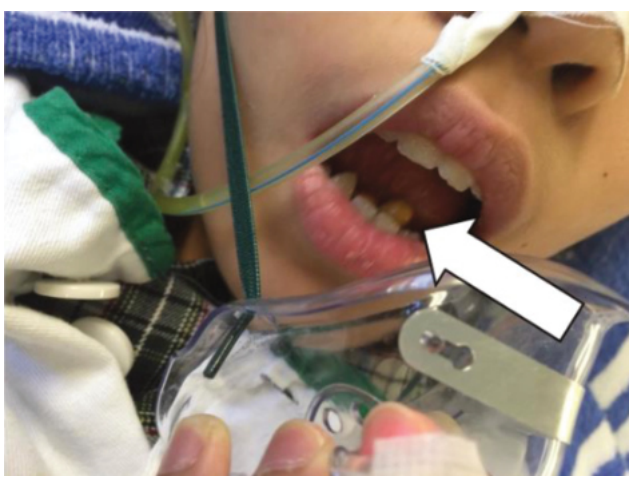

Figure 1 Sublingual capsular ATRA (white arrow).

diagnosis. She remained in clinical remission three years and four months after diagnosis. Her bone marrow aspirate showed morphological remission, and serial molecular surveillance remained negative for PML-RARA fusion.

Discussion

As the patient developed acute appendicitis with abscess formation and paralytic ileus, medications could not be given orally. Other non-oral dosage forms of ATRA e.g. intravenous or per-rectal, were not available worldwide. We were faced with two options, either omitting ATRA or giving it via another route.

Before the era of ATRA, APL patients were treated with cytotoxic agents only. A complete remission rate of 75-80% could be achieved.[2] However, the remission was not long-lasting. The median duration of remission ranged from 11 to 25 months, and only 35% to 45% of the patients could be cured by cytotoxic agents alone.[4] Also, a large proportion of patient succumbed in early stages of treatment due to fatal haemorrhages.

The discovery of ATRA, a differentiating agent, in the late 1970s revolutionised the treatment of APL. Studies were able to demonstrate the effect of ATRA on the prompt resolution of bleeding tendencies and induction of remission.[2] As a result, by the end of 1992, the European Cooperative Group considered any regimen for the treatment of APL that did not include ATRA to be unethical.[2]

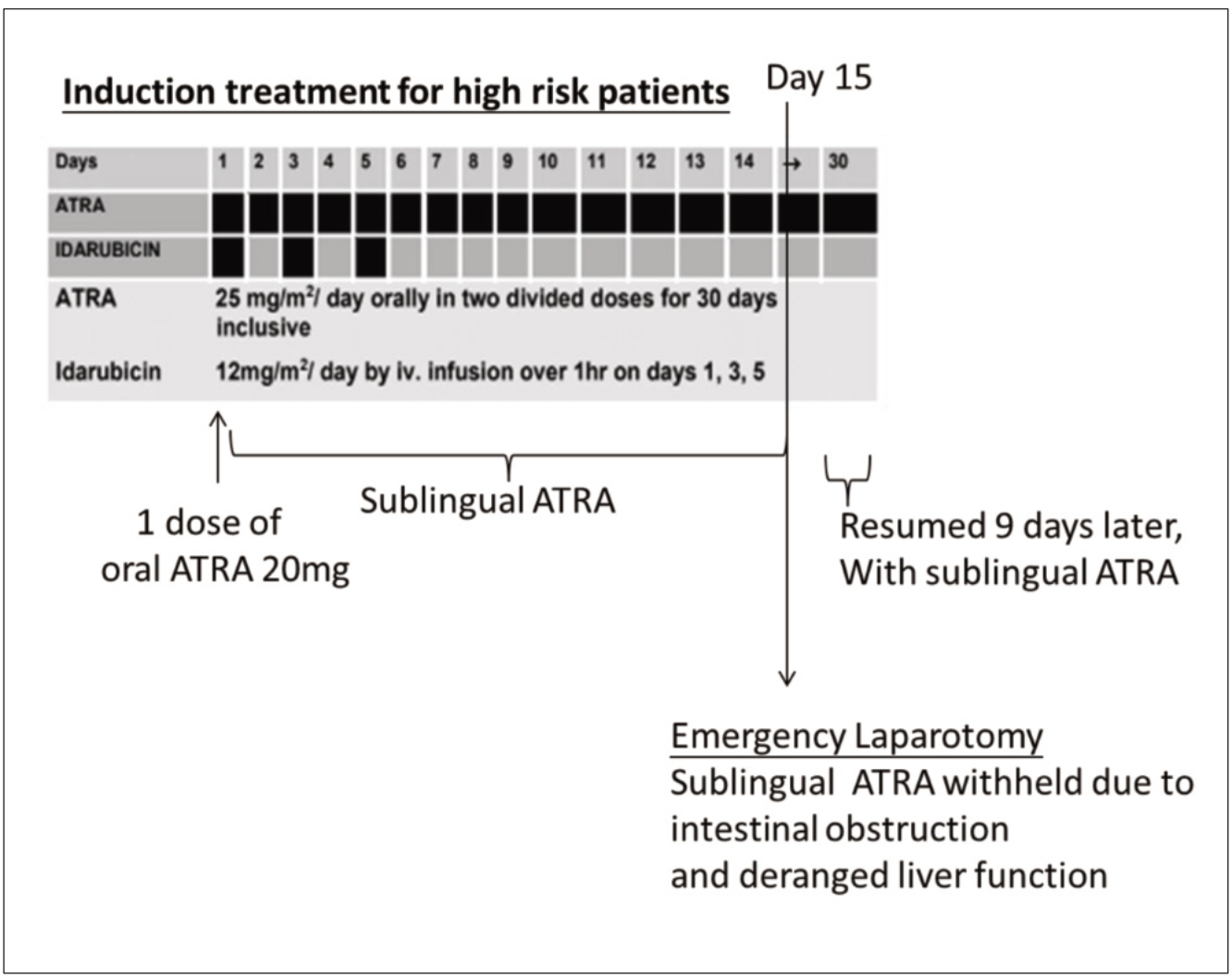

Figure 2 Summary of induction treatment.

In this day and age, after the introduction and optimisation of ATRA-based regimens, the complete remission rate was raised to 90% to 95% and 5-year disease-free-survival to 74%.[4] Thus worldwide, ATRA has become an integral part of APL treatment regimen for both adult and paediatric patients.

ATRA is manufactured as a 10 mg gelatin-encapsulated capsule (Figure 3). It cannot be administered via nasogastric tube as the capsule is too big to pass through. Its content is very viscous and thus cannot be administered via nasogastric tube as it will then stick to the wall of the tube. There were a few case reports[5,6] worldwide describing the difficulty of ATRA administration in various clinical situations, including to patients who could not swallow capsules either because of decreased consciousness or pre-existing dysphagia.

Kueh et al[7] reported the first successful induction by using sublingual ATRA in an adult male APL patient who was comatose because of intracranial haemorrhage in 1996. They milked the content of ATRA capsule onto the base of tongue twice a day. Subsequently, Mychajlonka et al[8] reported a trial of sublingual ATRA in a comatose adult female APL patient in 2017. Absorption of sublingual ATRA was demonstrated, with mean peak plasma concentrations between one and three hours after dosing with an elimination half-life of 30 to 120 minutes. The reason for such success is that ATRA is highly lipophilic,[9] which is preferred for sublingual absorption.[10]

All the reported cases of using ATRA sublingually involved opening the capsule and squeezing the content onto the tongue base of the patient. However, that posed occupational hazards to the medical personnel preparing the drug. Thus we resorted to putting a softened ATRA capsule on patient's tongue base. After 30 minutes, the capsule itself remained intact but empty as all the content was absorbed through the capsule by diffusion. Examination of the capsule was done every time after administration to ensure complete absorption. This is the first reported case of successful induction of clinical remission with sublingual capsular ATRA.

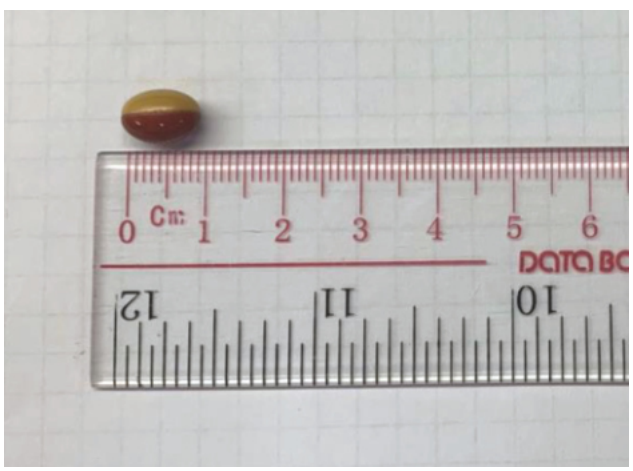

Figure 3 ATRA capsule.

In usual APL treatment, plasma ATRA level is not checked. Thus, despite several case reports, ours included, demonstrating the effect of sublingual ATRA in prompt resolution of DIC and eventual success in inducing remission, the subsequent serum ATRA level could not be compared with that following oral ATRA administration. After literature review, it was demonstrated once again that sublingual ATRA was only used in desperate and rare situations and no clear pharmacokinetic data (e.g. peak serum concentration, mean serum concentration, area under the curve, metabolic rate, half-life, etc.) was documented. Further discussion should be made for whether checking ATRA serum level is necessary and whether any target serum ATRA level should be aimed.

Conclusion

ATRA is an integral part of APL treatment, as demonstrated by decades of clinical trials. However, oral administration becomes difficult in patients who cannot swallow or tolerate oral medication for various reasons, as in our patient with surgical complications. We reported the first case of administrating softened ATRA capsule sublingually to a paediatric patient with achievement of remission after induction chemotherapy. Future studies checking serum ATRA level following sublingual administration, and comparison with that following oral route, would be needed to confirm sublingual capsular ATRA as a safe and practical recommended alternative to oral ATRA.

Declaration of Interest

None

References

1. Chan WYK, Lam GKS, Chiu JKH, Ku DTL, Ho KKH, Ha SY. Comparison on Treatment Outcomes on Paediatric Acute Promyelocytic Leukaemia: ICC APL 2001 Versus HKPHOSG AML 1996 Protocol. HK J Paediatr (new series) 2019;24:203-15.
2. Degos L. The history of acute promyelocytic leukaemia. Br J Haematol 2003;122:539-53.
3. Testi AM, Pession A, Diverio D, et al. Risk-adapted treatment of acute promyelocytic leukemia: results from the International Consortium for Childhood APL. Blood 2018;132:405-12.
4. Wang ZY, Chen Z. Acute promyelocytic leukemia: from highly fatal to highly curable. Blood, 2008;111:2505-15.
5. Takitani K, Nakao Y, Kosaka Y, et al. Low plasma level of all-trans retinoic acid after feeding tube administration for acute promyelocytic leukemia. Am J Hematol 2004;76:97-8.
6. Okumura LM, Baruel Okumura PC, Veroneze C. Administration of all-trans retinoic acid through enteral tubes in acute promyelocytic leukemia: the handling of cytotoxic agents and clinical benefits. Rev Bras Hematol Hemoter 2017;39:86-8.
7. Kueh YK, Liew PP, Ho PC, Wu TS. Sublingual administration of all-trans-retinoic acid to a comatose patient with acute promyelocytic leukemia. Ann Pharmacother 1999;33:503-5.
8. Mychajlonka C, Radosevich JC. Case report on the novel sublingual administration of all-trans retinoic acid in combination with intravenous arsenic trioxide for the treatment of newly diagnosed Acute Promyelocitic Leukemia. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy 2017;37:e124-238.
9. Narvekar M, Xue HY, Wong HL. A novel hybrid delivery system: Polymer-oil nanostructured carrier for controlled delivery of highly lipophilic drug all-trans-retinoic acid (ATRA). Int J Pharm 2012;436:721-31.
10. Narang N, Sharma J. Sublingual mucosa as a route for systemic drug delivery. International Journal of Pharmacy and Pharmaceutical Sciences 2011;3:18-22.