Successful Treatment by All-Trans Retinoic Acid in a Patient with Acute Promyelocytic Leukemia Complicated by Liver Cirrhosis and Polycystic Kidney

Arito Yamane1, Norifumi Tsukamoto1, Takayuki Saitoh1, Hideki Uchiumi1, Hiroshi Handa3, Masamitsu Karasawa2, Yoshihisa Nojima1 and Hirokazu Murakami1

Abstract

Although all-trans retinoic acid (ATRA) is widely used in acute promyelocytic leukemia (APL), there is little data as to whether or not ATRA is useful for patients with liver and renal failure. A 63-year-old APL patient, complicated by Child-Pugh class A liver cirrhosis and chronic renal failure (creatinine 3.2 mg/dL), was successfully treated with 45 mg/m²/day of ATRA. With three courses of chemotherapy, complete remission has been maintained for four years in this patient. Serum trough and maximum ATRA concentration, and the area under the curve (AUC) were not elevated. These observations suggest that full-dose ATRA therapy might be safely applicable to such a complicated case with APL.

Key words: acute promyelocytic leukemia, all-trans retinoic acid, renal failure, liver cirrhosis, hypercalcemia

Introduction

Acute promyelocytic leukemia (APL) has become one of the most curable forms of leukemia by treatment with all-trans retinoic acid (ATRA) (1). ATRA can induce terminal differentiation and apoptosis of leukemia cells resulting in high rates of complete remission (CR) (1, 2). Although ATRA has been widely used, little data is available concerning patients with liver or renal dysfunction (3, 4). Here, we report a Japanese APL patient with both liver and renal dysfunction, who achieved complete remission by ATRA; this case was also complicated with hypercalcemia during the treatment. In addition, we tried to assess the serum ATRA levels with reference to the clinical course.

Case Report

A 63-year-old man, who had been suffering from liver cirrhosis due to hepatitis C virus infection for 10 years, was admitted to our hospital because of pancytopenia in late May, 2004. He had a family history of polycystic kidney disease (PKD) in his mother and sisters. On physical examination, his liver and spleen were palpable 6 cm and 3 cm below the costal margin, respectively, and his kidneys were enlarged. Laboratory data were hemoglobin level (Hb) 8.9 g/dL, platelet count (PLT) 28×109/L, white blood count (WBC) 0.6×109/L with 14% neutrophils and 83% lymphocytes, prothrombin time (PT) 70%, fibrinogen 208 mg/dL, APTT 28.3 sec, fibrinogen degenerative product (FDP) 14.4 µg/mL, anti-thrombin 67%, total bilirubin 0.7 mg/dL, albumin 3.6 g/dL, aspartate transaminase (AST) 10 IU/L, alanine transaminase (ALT) 8 IU/L, lactate dehydrogenase (LDH) 91 IU/L, alkaline phosphatase 166 IU/L, gamma-glutamyl transpeptidase (γ-GTP) 56 IU/L, choline esterase (ChE) 3.0×103 IU/L (normal 4.5-10), indocyanine green retention rate at 15 minutes (ICG R15) 15%, blood urea nitrogen (BUN) 47 mg/dL, creatinine 3.2 mg/dL, and creatinine clearance 18.0 mL/min. Abdominal echogram and computed tomography (CT) scan demonstrated enlarged liver, kidney and spleen with polycystic lesions in his kidney and liver, but ascites was not observed. Bone marrow examination re-

Figure 1. Clinical course of the present case.

Table 1. Pharmacokinetic Parameters of All-trans Retinoic Acid (ATRA)

<table>
<thead>
<tr>
<th>Patient</th>
<th>ATRA (ng/mL)</th>
<th>AUC (ng/mL/hr)</th>
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<tbody>
<tr>
<td>day 1</td>
<td>before 0.6</td>
<td>158.8</td>
</tr>
<tr>
<td></td>
<td>2 hr 49.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 hr 21.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 hr 2.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16 hr &lt;0.5</td>
<td></td>
</tr>
<tr>
<td>day 8</td>
<td>before 0.5</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>2 hr 0.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 hr 12.4</td>
<td></td>
</tr>
<tr>
<td>day 26</td>
<td>before 1.6</td>
<td>NA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Control</th>
<th>ATRA (ng/mL)</th>
<th>AUC (ng/mL/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(45 mg/m²/day)</td>
<td>1.84±0.33</td>
<td>537±191</td>
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<table>
<thead>
<tr>
<th>APL patients (trough)</th>
<th>ATRA (ng/mL)</th>
<th>AUC (ng/mL/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(45 mg/m²/day)</td>
<td>1.84±0.33</td>
<td>537±191</td>
</tr>
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NA: not available

vealed 64.4% of abnormal promyelocytes, which occasionally contained Auer bodies. Chromosomal analysis revealed 46XY, t (15;17) (q22;q21), +8 and the PML/RARα fusion mRNA were detected. A diagnosis of APL complicated by liver cirrhosis classified as Child-Pugh class A and chronic renal failure due to PKD was established.

Although the use of ATRA has been prohibited for patients with either liver or renal dysfunction, the ATRA monotherapy at a dose of 45 mg/m²/day was started in the present patient because no other appropriate treatment was available (Fig. 1). Subsequently, WBC gradually increased. The serum concentration of ATRA on days 1 and 8, measured by HPLC analysis (SRL, Tokyo, JAPAN) (5, 6), are listed in Table 1 (Table 1). On day 1, the half-life (T1/2) was normal (0.96 hr), but the maximum drug concentration (Cmax) and the area under the curve (AUC) were 49.1 ng/mL and 158.8 ng/mL/hr, respectively, which were relatively low compared to reported APL patients (294±89 ng/mL and 537±191 ng/mL/hr, respectively) (5-7). Trough ATRA concentration on day 8 was not raised. Although he had a mild headache, he showed no further evidence of ATRA syndrome.

However, on day 26, his serum adjusted calcium concentration was elevated to 13.8 mg/dL; at that time, the trough concentration of ATRA was not elevated (1.6 ng/mL) and serum phosphate was normal. Parathyroid hormone (PTH) and 1,25 (OH)₂D, were slightly depressed (8.0 pg/mL and 3.4 pg/mL, respectively), and PTH-related protein (PTH-rP) was not detected. ATRA therapy was discontinued and he was treated with saline, diuretics, pamidronate, and etaceton. On day 30, as serum calcium concentration decreased to normal, approximately half dose of ATRA treatment was re-started; but leukemia blasts remained in his bone marrow. So, the dose was increased to 45 mg/m²/day with administration of pamidronate on day 35. Although serum creatinine elevated temporarily to 4.8 mg/dL, no further elevation of calcium concentration occurred while receiving this dosage of ATRA. The patient attained complete remission (CR) with disappearance of abnormal chromosome karyotype and PML/RARα fusion gene on fluorescence in situ hybridization analysis on day 53. The patient received three courses of anthracycline mono-therapy as consolidation therapies: MIT 7 mg/m² 3 days, DNR 50 mg/m² 3 days, and IDR 12 mg/m² 3 days, respectively. During these therapies,
Figure 2. CT image on day 190 in febrile neutropenia. Ascites, splenomegaly, and polycystic lesions on the liver and kidney are presented.

transient elevation of serum creatinine (5.0 mg/dL, on day 86), elongation of PT up to 50% (on day 185), and ascitic fluid on CT were observed (on day 190) in association with febrile neutropenia (Fig. 2), but they recovered by the end of these therapies. While he is now receiving hemodialysis due to the progression of PKD from 2006, the patient remains in complete remission for more than four years without maintenance therapy.

Discussion

One of the most characteristic features in the present case is that an APL patient, complicated by chronic renal failure and liver cirrhosis, can achieve molecular complete remission by full-dose ATRA treatment; this is the first such case because an appropriate dose of ATRA has not been previously suggested for such cases. ATRA, derivative of vitamin A, is known to be metabolized to produce 4-oxo ATRA, 4-oxo 13-cis retinoic acid, and many isomers by chromosome P-450-like enzyme in the liver, which is excreted as a glucuronide form in the bile (2/3) and urine (1/3) (6, 7). Whether ATRA will accumulate in such patients with liver and renal dysfunction is a matter of interest, as an accumulation of vitamin A in some patients with hemodialysis (HD) has been reported (8, 9); in addition, most of renal dysfunction in APL has been reported as a part of an ATRA syndrome or a thrombotic complication in disseminated intravascular coagulation (DIC), where organ dysfunctions might be temporal and could be overcome by induction of HD (10). The trough ATRA concentration on days 1, 8 and 26, measured by HPLC, were not raised and its resultant AUC was relatively low compared to normal individuals suggesting no storage of ATRA in this patient. Some reports indicated no significant elevation of ATRA in APL patients receiving HD irrespective of HD or non-HD day (3, 4).

As for liver function, ATRA has become one of the potential candidates for treatment of liver cirrhosis because it suppresses liver fibrosis through reduction of production of transforming growth factor β 1 (TGF β-1), interleukin 6, and type I collagen (11, 12). Therefore, liver cirrhosis itself might not be a contra-indication of ATRA. On the contrary, anthracyclines are sometimes considered to be toxic for patients with hepatic dysfunction, but we were able to accomplish consolidation therapies without worsening liver function. Therefore, ATRA therapy followed by consolidation therapies consisting of anthracyclines might be one of the therapeutic options to be considered in patients with chronic both hepatic and renal dysfunction with careful management. The relatively low Cmax and AUC in this patient can be explained by the fact that pharmacokinetics of ATRA might be influenced by gastrointestinal absorption and metabolism in the liver (5-7). These results can also account for the insufficiency of a half dose of ATRA administration; full dose of ATRA was needed to achieve CR in the present case.

Another characteristic in the present case is that he was complicated by hypercalcemia. Hypercalcemia in ATRA therapy has been reported (13-15), and there are several substances that increase serum calcium levels; PTH, PTH-rP, prostaglandins, and vitamin D metabolites (14, 15). In our case, vitamin D, PTH, and PTH-rP levels were not elevated, which exclude the possibility of primary hyperparathyroidism and ectopic PTH secretion. One possibility is that metabolite of ATRA, such as 4-oxo trans retinoic acid or 13-cis retinoic acid might accumulate in plasma, resulting in hypercalcemia (2, 5). However, as we did not analyze these metabolites’ the precise mechanism is uncertain in this case. Bisphosphonate is effective for improvement of hypercalcemia (15). One of the limitations of bisphosphonate is that this may be influenced by renal dysfunction (15, 16). However, the recent guideline describes there is no need to change the dosage in the use of pamidronate among patients with renal impairment (16). Based on these findings, we were successfully able to administrate pamidronate without dose reduction of ATRA, but monitoring of renal function was necessary.

In conclusion, contrary to previous reports where ATRA is not recommended for patients with either liver or renal dysfunction, full dose ATRA therapy was applicable for an APL patient complicated by liver cirrhosis and renal failure not on hemodialysis. As dose reduction of ATRA is sometimes necessary in patients with renal failure (4, 17), careful management is essential.

References


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