Successful Continuous Treatment with All-Trans Retinoic Acid for Acute Promyelocytic Leukemia; Secondary Malignancy after the Treatment of Osteosarcoma

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We report a rare case of complete remission for 32 months with continuous treatment with all-trans retinoic acid (ATRA) alone in a patient with acute promyelocytic leukemia which developed as a second malignancy after the treatment of osteosarcoma after failure of conventional chemotherapy. The adverse effects of ATRA were apparently tolerable. (Internal Medicine 33: 654–657, 1994)

Key words: etoposide, long complete remission

Introduction

Sixty-four or 96% of patients with acute promyelocytic leukemia (APL) enter complete remission upon treatment with all-trans retinoic acid (ATRA) (1, 2). However, the duration of complete remission is generally brief, and relapse occurs despite continuous ATRA treatment (1, 2).

We report a rare patient with APL, second malignancy after the treatment of osteosarcoma, who had been in complete remission (CR) for 32 months with the continuous treatment of ATRA alone after failure of conventional chemotherapy.

Case Report

A 13-year-old male who developed osteosarcoma at the right distal femur underwent excision and replacement of the right knee joint in August 1987. At the age of 14 years, he developed lung metastasis and underwent a right lower lobectomy of the lung in November 1988. When he was 15 years old osteosarcoma recurred at the right femur and was excised. At the age of 16 years, the patient developed lung metastasis and underwent left lower lobectomy in November 1989. Chemotherapy was performed throughout the entire course of treatment. When the patient was 17 years old, severe pancytopenia was identified, and he was referred to the Second Department of Internal Medicine, Mie University Hospital with extensive purpura in April 1991. The total accumulative doses of chemotherapeutic agents administrated at the orthopedic department were as follows: methotrexate, 430 g/m²; vincristine, 16 mg/m²; bleomycin, 187 mg/m²; cyclophosphamide (CPA), 84 g/m²; Dactinomycin, 8.9 g/m²; Adriamycin (ADR), 540 mg/m²; cis-platinum, 360 mg/m²; and etoposide, 300 mg/m².

Acute promyelocytic leukemia (APL) with disseminated intravascular coagulation (DIC) was diagnosed (Table 1). Chromosomal karyotype of bone marrow cells was 46XY, t(15;17). We started induction therapy with enocitabine at 300 mg/day × 10 days, daunorubic in at 70 mg/day × 7 days, 6-mercaptopurine at 100 mg/day × 10 days, and prednisolone at 60 mg/day × 4 days, as well as therapy for DIC with gabexate mesilate from

<table>
<thead>
<tr>
<th>Table 1. Laboratory Data on Admission to Our Department</th>
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<tbody>
<tr>
<td><strong>Peripheral blood</strong></td>
</tr>
<tr>
<td>RBC</td>
</tr>
<tr>
<td>Hb</td>
</tr>
<tr>
<td>Ht</td>
</tr>
<tr>
<td>Plat</td>
</tr>
<tr>
<td>WBC</td>
</tr>
<tr>
<td>Seg</td>
</tr>
<tr>
<td>Lym</td>
</tr>
<tr>
<td>APL cell</td>
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<tr>
<td><strong>Bone Marrow</strong></td>
</tr>
<tr>
<td>NCC</td>
</tr>
<tr>
<td>M/E</td>
</tr>
<tr>
<td>APL cell</td>
</tr>
<tr>
<td>Karyotype</td>
</tr>
<tr>
<td>Blood chemistry</td>
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<td>TP</td>
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April 10, 1991 (Fig. 1). However, this treatment caused severe bone marrow hypoplasia. He developed cerebral bleeding and sepsis. Recombinant human granulocyte colony stimulating factor was used for the bone marrow recovery but increased the APL cell number, and the induction regimen was therefore considered to be ineffective. ATRA at a dose of 90 mg/day was used as alternative induction therapy from April 28, 1991, and the patient was also receiving gabexate mesylate for DIC and antibiotics for sepsis. As he developed hyperleukocytosis (WBC; 31,180/µl) and jaundice, ATRA was discontinued on May 8, 1991, and Ara-C at 80 mg/day was administrated for 2 days to counter hyperleukocytosis. After 2 days, when the value of total bilirubin began to decrease, ATRA therapy at 60 mg/day was begun again from May 17, 1991. After 5 days of ATRA therapy DIC was improved. After 29 days of ATRA therapy, in June 1991, he entered complete remission. The karyotype of bone marrow cell chromosomes became normal 29 days after the initial ATRA treatment. The patient, who had been on maintenance therapy with ATRA at 40 mg/day, had been in CR and healthy for 32 months. APL relapsed in February 1994.

Discussion

After the induction into complete remission with ATRA, it was not replaced with conventional chemotherapy as post-remission chemotherapy because the patient’s liver and renal function was impaired and because the first induction chemotherapy regimen had been ineffective. He had received multiple high doses of chemotherapeutic agents for osteosarcoma, including 675 mg/m² of ADR. As we were concerned about the cumulative effect of anthracycline (3), we did not consider conventional chemotherapy but rather opted to continue ATRA as maintenance therapy. APL patients maintained with ATRA alone have been reported to relapse earlier and have poor sensitivity to ATRA after relapse (1, 2). However, in the present very rare case, our patient had been in CR with ATRA alone for about 32 months. Although the plasma ATRA level is reported to be reduced in the ATRA-resistant patient with APL, the mechanism of reduction is not known (4). Although the plasma ATRA level in our patient was not examined, we speculate that his poor liver function may contribute to high the plasma level of ATRA.

The development of leukemia as a second malignancy after treatment of a childhood malignancy is well known, but its
velop unexplained pancytopenia after receiving combined therapy should be considered in patients with osteosarcoma who de-
may become a more frequent complication. This possibility
improve survival, therapy-linked acute myelogenous leukemia
osteosarcoma has recently become more intensive in an effort
APL may require further investigation. Since the treatment of
etoposide for Langerhans' cell histiocytosis of bone (21). Our
translocation). Haupt et al reported the first case of secondary
relationship with secondary acute myelocytic leukemia
inclusion varies with the type of primary tumor. The relative
risk ratio of leukemia for a patient whose primary tumor is
Hodgkin's disease is 89 and 8.3 for osteosarcoma (5–10). Thus,
leukemia in a patient with osteosarcoma as the primary tumor is
relatively rare, with only a few cases having been reported
(11–14) (Table 2). Secondary APLs are relatively rare and
occupy only 1 and 4.1% of all secondary leukemia after chemo-
therapy and/or radiotherapy for Hodgkin's disease and all
malignant disease, respectively (15, 16). The present case is the
first reported case to our knowledge in a patient with APL
related to chemotherapy for osteosarcoma. The median dura-
tion from the treatment of the first tumor until the development of
therapy-linked leukemia is generally 4–5 years, but that in
patients with osteosarcoma as the first tumor is 30 months
(Table 2). In the present patient, this interval was 4 years. In
addition to alkylating agents and procarbazine originally postu-
lated to be leukemogenic drugs, etoposide was suggested as a
causal relationship with secondary acute myelocytic leukemia
(17–20). The characteristics of secondary acute myelocytic
leukemia after etoposide treatment are reported to be: 1) a
shorter latency period (2–3 years), 2) lack of a preleukemic
phase, 3) more frequent occurrence of FAB subtype M4 or M5,
and 4) peculiar cytogenetic constitution (often involving 11q23
translocation). Haupt et al reported the first case of secondary
APL (variant type) after single-agent chemotherapy with
etoposide for Langerhans' cell histiocytosis of bone (21). Our
patient had been treated with 300 mg/m² of etoposide. The
relationship with etoposide and secondary AML, especially
APL may require further investigation. Since the treatment of
osteosarcoma has recently become more intensive in an effort
to improve survival, therapy-linked acute myelogenous leukemia
may become a more frequent complication. This possibility
should be considered in patients with osteosarcoma who de-
velop unexplained pancytopenia after receiving combined
modality therapy.

Table 2. Therapy-Linked Acute Leukemia after Treatment of Osteosarcoma

<table>
<thead>
<tr>
<th>Type</th>
<th>Age</th>
<th>Sex</th>
<th>Chemotherapy for osteosarcoma</th>
<th>Radiation (Gy)</th>
<th>Interval (month)</th>
<th>Effect on leukemia</th>
<th>Survival (month)</th>
<th>Chromosome (blast cell)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMMoL</td>
<td>28</td>
<td>F</td>
<td>ADR, VCR, MTX</td>
<td>3.5</td>
<td>46</td>
<td>NR</td>
<td>8</td>
<td>46XX</td>
<td>(11)</td>
</tr>
<tr>
<td>AMoL</td>
<td>14</td>
<td>M</td>
<td>ADR, BLM, CPA, DCT</td>
<td>–</td>
<td>30</td>
<td>CR</td>
<td>7+</td>
<td>48XY,dup 1,3,+9</td>
<td>(12)</td>
</tr>
<tr>
<td>AMMoL</td>
<td>17</td>
<td>F</td>
<td>ADR, BLM, CPA, MTX, Act-D</td>
<td>–</td>
<td>25</td>
<td>CR</td>
<td>1.5+</td>
<td>47XX,+8,t(9;11)</td>
<td>(13)</td>
</tr>
<tr>
<td>ALL</td>
<td>14</td>
<td>M</td>
<td>ADR, VCR, MTX, IFO, ETO, CBDDA</td>
<td>–</td>
<td>9+7</td>
<td>CR</td>
<td>4</td>
<td>47XY,+6,t(4;11)</td>
<td>(14)</td>
</tr>
<tr>
<td>APL</td>
<td>13</td>
<td>M</td>
<td>ADR, VCR, MTX, ETO, DCT, CDDP,</td>
<td>–</td>
<td>48</td>
<td>CR</td>
<td>32+</td>
<td>46XY,t(15;17)</td>
<td>Our case</td>
</tr>
</tbody>
</table>

1) Interval between onset of osteosarcoma and acute leukemia.
2) NR: no response, CR: complete remission.
3) 47,XX,+8,t(9;11) (9 metaphases); 48XX,+8,+13,t(9;11) (8 metaphases); 46XX,t(9;11)(p21;q23) (7 metaphases).
4) 47,XY,+6,t(4;11)(q21;q23) (6 metaphases); 47,XY,+6,t(1;8)(p36;q13);t(4;11)(q21;q23) (6 metaphases).

References

17) Ratain J, Kaminer LS, Bitran J, et al. Acute nonlymphocytic leukemia following etoposide and cisplatin combination chemotherapy for ad-
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