Case Report

Successful Treatment of Myeloid Sarcoma in an Elderly Patient with Myelodysplastic Syndrome with Reduced-Dose Azacitidine

Kazuya Sato,1 Nodoka Tsukada,1 Junki Inamura,1 Shigetsuna Komatsu,2 Keisuke Sato,3 Masayo Yamamoto,4 Motohiro Shindo,4 Kentaro Moriichi,4 Yusuke Mizukami,4 Mikihiro Fujiya,4 Yoshihiro Torimoto,4 and Toshikatsu Okumura4

1Department of Hematology/Oncology, Asahikawa Kosei General Hospital, 1-24, Asahikawa 078-8211, Japan
2Department of Dermatology, Asahikawa Kosei General Hospital, 1-24, Asahikawa 078-8211, Japan
3Department of Clinical Laboratory, Asahikawa Kosei General Hospital, 1-24, Asahikawa 078-8211, Japan
4Division of Gastroenterology and Hematology/Oncology, Department of Medicine, Asahikawa Medical University, Asahikawa, Hokkaido, Japan

Correspondence should be addressed to Kazuya Sato; satofam@wine.plala.or.jp

Received 16 November 2020; Revised 6 April 2021; Accepted 13 April 2021; Published 22 April 2021

1. Introduction

Myeloid sarcoma (MS), which involves extramedullary lesions, is classified as a unique subtype of acute myeloid leukemia (AML). At present, no standard treatments for MS have been established. The patient was an 89-year-old man with myelodysplastic syndrome-excess blast-2 (MDS-EB-2) with a 2-year history of intermittent treatment with azacitidine (AZA) during a 4-year history of MDS. He developed painful cutaneous tumors 8 months after the second discontinuation of AZA. They were refractory for antibiotics and topical tacrolimus hydrate. A tumor biopsy was performed, and the histological findings of the tumor lesion showed a proliferation of tumor cells that were positive for myeloperoxidase and CD68 and negative for CD4 and CD123. The patient was diagnosed with MDS-associated MS. MDS-EB-2 quickly progressed to AML with the appearance of peripheral blood blasts and 25% bone marrow blasts. Monotherapy with reduced-dose AZA (37.5 mg/m2 for 7 days, every 4–6 weeks) was restarted, and the MS quickly disappeared. The patient’s MS was successfully treated with 16 cycles of AZA treatment over a 22-month period. There have been 10 reported cases in which MS was successfully treated with AZA. Among the 10 cases, the patient in the present case was the oldest. Treatment with reduced-dose AZA should be considered as a therapeutic option for MS in elderly patients with MDS, especially patients who are ineligible for intensive chemotherapy.
An 85-year-old man with pancytopenia was diagnosed with MDS with multilineage dysplasia (MDS-MLD) based on bone marrow aspiration (BMA), which revealed 2.6% myeloblasts with trilineage dysplasia and normal karyotype. Based on these findings, the case was categorized as intermediate-1 or low risk according to the International Prognostic Scoring System (IPSS) [14] or Revised IPSS (IPSS-R) [15], respectively. At this point, the patient had been treated with vitamin K2 (menatetrenone) and active vitamin D3 (calcitriol) because combination therapy of these two drugs was reported to be effective against low-risk MDS [16]. At 87 years of age, the patient undertook BMA again because his pancytopenia had progressed, and he was diagnosed with MDS with excess blasts-2 (MDS-EB-2) based on the BMA findings, which revealed 11% myeloblasts and multilineage dysplastic changes of bone marrow cells (Figures 1(a)–1(d)), with a normal karyotype. The disease status was categorized as intermediate-2 risk according to the IPSS and high risk according to the IPSS-R; thus, AZA treatment was initiated on hospitalization at the standard dose of 75 mg/m²/day, subcutaneously, for 7 days every month. The patient achieved a hematological improvement (HI) with manageable adverse events (AEs), including constipation and general malaise after the first cycle of AZA. The second cycle was therefore administered in an outpatient setting. However, the treatment was discontinued due to septic shock after the second cycle of AZA. The patient became dependent on red blood cell (RBC) transfusions due to a clinical progression of MDS because one year after the discontinuation of AZA (at 88 years of age), we did not perform any histological examinations, such as BMA. Therefore, additional 3 cycles of AZA were administered in an outpatient setting with a reduced dose of 37.5 mg/m² (50% dose reduction) daily. The dose of AZA was decided according to the prescribing information for AZA [17] based on the nadir absolute neutrophil count <0.5 × 10⁹/L in the preceding (second) cycle. Treatment with AZA was discontinued again because the patient refused to continue the treatment due to the AEs, which included constipation and general malaise, as well as the inconvenience of going to the hospital. At eight months after the second discontinuation of AZA (at 89 years of age), a painful cutaneous tumor, the top of which showed yellow-colored necrosis (Figure 2(a)), developed at the left groin lesion. Laboratory tests revealed the following: white blood cell count, 2,900/μL, with 63.6% neutrophils, 32.6% lymphocytes, 3.5% monocytes, 0.3% eosinophils, and no blast cells; hemoglobin, 6.6 g/dL; platelet count, 8.7 × 10⁹/μL; and C-reactive protein, 0.57 mg/dL. No treatments, including oral and topical antibiotics, topical tacrolimus hydrate, and analgesics, had any effect on the tumor. A biopsy of the tumor was performed one month after its development. Histological examination revealed the proliferation of tumor cells with a high nuclear/cytoplasmic ratio (Figure 3(a)). Immunohistochemically, the neoplastic cells were positive for myeloperoxidase (Figure 3(b)), partially positive for cluster of differentiation (CD) 68 (Figure 3(c) and CD33, but negative for CD3, CD4 (Figure 3(d)), CD20, CD34, CD56, CD117, and CD123 (Figure 3(e)). A diagnosis of MDS-associated MS was made.

Considering the patient’s age, clinical conditions, and the previously experienced AEs, treatment with AZA was started again at a dose of 37.5 mg/m²/day, subcutaneously, for 7 days every 4–6 weeks (in total, this was the 6th cycle of AZA treatment) during short-term hospitalization, which consisted of 9 days of inpatient treatment per cycle, in order to manage the acute-phase AEs caused by AZA. The cutaneous MS lesion located on the left groin (Figures 4(a)–4(c)) and that on the left cheek (Figures 4(d)–4(f)) promptly disappeared after the 6th and 7th cycles of AZA treatment. Although myeloblasts had appeared in peripheral blood after several cycles of retreatment with AZA, the treatment was continued because of persistence of the response on MS, and the pain caused by his lesions remained relieved, with tolerable AEs, by AZA. The patient had received 16 cycles (over a 22-month period) of AZA treatment with the same dose on repeated short-term hospitalization until he died of progression of AML. He eventually received 21 cycles of AZA treatment in total. No exacerbation of cutaneous MS had been confirmed during AZA treatment.

3. Discussion

We experienced a case of MS in an elderly man with MDS, which was successfully treated with AZA over a 22-month period. Although cytarabine-based intensive chemotherapy is generally selected as the initial therapy for MS (based on its efficacy) [2, 3], the patient in the present case was 89 years of age, and there were concerns about AEs. Radiation therapy may be a therapeutic option for MS; however, the patient had already developed multiple MS lesions; thus, it was not selected. For these reasons, reduced-dose AZA monotherapy was restarted again, and AZA-associated AEs were managed by short-term hospitalization. While the present patient was expected to have an approximately 2-year survival after starting AZA treatment, based on the result of the AZA-001 phase III trial for higher-risk MDS (median overall survival of 24.5 months) [5], he received 21 cycles of AZA treatment in total and eventually survived for 49 months despite developing MS.

To our knowledge, there are 10 reported cases in which MS including leukemia cutis (LC), a phenotype of
extramedullary leukemia induced by the infiltration of leukemic cells into the epidermis, the dermis, or the subcutis [18], was successfully treated with AZA [8–13]. The clinical characteristics of the cases are shown in Table 1. Aside from two cases, most were elderly patients; our patient was the oldest. In all of these cases, AZA treatment was performed for MS that developed in a patient with preceding hematological malignancies (MDS, chronic myelomonocytic leukemia.

**Figure 1:** Microscopic findings of the bone marrow smears. Bone marrow aspirate smears (May–Giemsa staining; magnification: ×400) showed (a) myeloblasts (arrows) and a hyposegmented mature neutrophil (arrowhead), (b) a binucleated erythroblast, and (c) a micromegakaryocyte (indicated with a star). (d) Myeloperoxidase staining (magnification: ×400) of the bone marrow cells showed a hypogranular neutrophil (indicated with an asterisk).

**Figure 2:** Cutaneous tumor lesions. (a) A painful cutaneous tumor, the top of which showed yellow-colored necrosis, which developed at the left groin 8 months after the second discontinuation of azacitidine. (b) Another cutaneous tumor, which appeared on the left cheek one month after the development of the first cutaneous lesion at the left groin.
Figure 3: The histological findings of the tumor located in the left groin. A biopsy specimen showed the proliferation of tumor cells with a high nuclear/cytoplasmic ratio on hematoxylin and eosin staining (×20) (a). Immunohistochemical staining (×20) of tumor cells was positive for myeloperoxidase (b), partially positive for cluster of differentiation (CD) 68 (c), negative for CD4 (d), and negative for CD123 (e).

Figure 4: Continued.
Figure 4: The response of cutaneous myeloid sarcoma (MS) to treatment with azacitidine. An MS located at the left groin before the first (6th in total) cycle of azacitidine retreatment (a). Before the second (7th in total) cycle (b). After the second cycle (c). An MS on the left cheek before the first cycle (d). Before the second cycle (e). After the second cycle (f).

Table 1: The clinical characteristics of cases of myeloid sarcoma that were successfully treated with azacitidine.

<table>
<thead>
<tr>
<th>Case/reported year</th>
<th>Age/sex</th>
<th>Diagnosis at development of MS</th>
<th>Sites of origin</th>
<th>Treatment for MS</th>
<th>Cycles of AZA for MS</th>
<th>Maximum response of AZA for MS</th>
<th>Outcome (cause of death)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (2013) 62/M</td>
<td>CMML type-2</td>
<td>Right humerus</td>
<td>AZA (75 mg/m² × 7 days) + RT (25 Gy) IDR + Ara C followed by allo-HSCT → CLAG followed by DLI and RT → a cycle of AZA (32 mg/m² × 5 days) → 4 cycles of AZA (75 mg/m² × 7 days) → RT</td>
<td>6°</td>
<td>Decreased in size</td>
<td>Alive</td>
<td>[8]</td>
<td></td>
</tr>
<tr>
<td>2 (2013) 34/M</td>
<td>Monoblastic leukemia cutis</td>
<td>Multiple skin nodules, groin mass</td>
<td>GO → FLAG and DLI → AZA (75 mg/m² × 5 days) 36 cycles of AZA (75 mg/m² × 5 days) for MDS → 41 cycles of the same dose of AZA after the onset of LC</td>
<td>5</td>
<td>Decreased in size</td>
<td>Died (multiorgan failure)</td>
<td>[9]</td>
<td></td>
</tr>
<tr>
<td>3 (2013) 39/F</td>
<td>Relapse of AML-M2 after allo-HSCT</td>
<td>Gingiva</td>
<td>AZA (75 mg/m² × 7 days) → 6-MP 9 cycles of AZA (75 mg/m² × 5 days) for CMML → 4 cycles of AZA (75 mg/m² × 7 days) after the onset of LC</td>
<td>17°</td>
<td>Pathological resolution</td>
<td>Alive</td>
<td>[9]</td>
<td></td>
</tr>
<tr>
<td>4 (2015) 72/M</td>
<td>MDS EB-2</td>
<td>Disseminated skin papules (LC)</td>
<td>AZA (75 mg/m² × 7 days) → 6-MP 9 cycles of AZA (75 mg/m² × 5 days) for CMML → 4 cycles of AZA (75 mg/m² × 7 days) after the onset of LC</td>
<td>41°</td>
<td>Regression of LC</td>
<td>Died (N/A)</td>
<td>[10]</td>
<td></td>
</tr>
<tr>
<td>5 (2015) 78/M</td>
<td>MDS MLD</td>
<td>Multiple skin lesions (LC)</td>
<td>DNR + Ara C → AZA (100 mg/body × 7 days, as maintenance therapy)</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 (2015) 76/M</td>
<td>CMML type-1</td>
<td>Multiple skin lesions (LC)</td>
<td>CAG → AZA (75 mg/m² × 7 days)</td>
<td>At least 1</td>
<td>Decreased in size</td>
<td>Died (AML progression)</td>
<td>[11]</td>
<td></td>
</tr>
<tr>
<td>7 (2016) 80/F</td>
<td>MDS → AML</td>
<td>Left eyelid</td>
<td>CAG → AZA (75 mg/m² × 7 days)</td>
<td></td>
<td></td>
<td>Skin: clinical and radiological resolution; others: a marked reduction in the FDG uptake on PET-CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 (2017) 71/F</td>
<td>MDS EB-2</td>
<td>Nasopharynx, tonsil, spleen, multiple lymph nodes, skin</td>
<td>DNR + Ara C → AZA (100 mg/body × 7 days, as maintenance therapy)</td>
<td>20°</td>
<td></td>
<td>Alive</td>
<td>[12]</td>
<td></td>
</tr>
</tbody>
</table>
AZA treatment was effective for MS originating at various sites; 7 cases (including our case) involved skin lesions. Four cases (cases 1 and 7–9) with MS were successfully treated with AZA in combination with sequential radiotherapy, multidrug chemotherapy, or biomodulatory drugs. One of the 4 cases (case 8) was treated with AZA as a maintenance therapy. Including the present case—in which AZA monotherapy was administered for remission induction and maintenance therapy—six cases (cases 2–6 and 10) with MS were successfully treated with AZA in combination with AZA as a maintenance therapy. Five of them had skin leukemic lesions (LC) with MS; 6 of the patients eventually died of the progression of leukemia, but the exacerbation of the skin lesions was not observed during the treatment. (The dose of AZA was reduced in 4 cases) 

AZA treatment might differ by disease status or histology of the dose. Although further accumulation of such cases is required to clarify this issue.

However, a case of LC has been reported in a patient with acute myelomonocytic leukemia on AZA treatment [26]. That case was considered refractory to the AZA treatment. The responsiveness of cutaneous lesions of MDS/AML to AZA treatment might differ by disease status or histology of underlying disease. Physicians should consider the possibility of such a case developing.

We did not have a good treatment plan for this patient other than repeating the treatment with AZA. Venetoclax, which is an inhibitor of the antiapoptotic BCL2 protein, is reported to be clinically beneficial in hypomethylating agent-(HMA-) resistant patients with MDS/AML in combination with an HMA [27]. While venetoclax is not currently available for patients with MDS/AML in our country, combination therapy of venetoclax and AZA will likely be a good treatment option for patients such as the present case.

### 4. Conclusion

We reported a case of MS that developed in an elderly patient with MDS, which was successfully treated with AZA monotherapy for a 22-month period, despite a reduction in the dose. Although further accumulation of such cases is

### Table 1: Continued.

<table>
<thead>
<tr>
<th>Case/report year</th>
<th>Age/sex</th>
<th>Diagnosis at development of MS</th>
<th>Sites of origin</th>
<th>Treatment for MS</th>
<th>Cycles of AZA for MS</th>
<th>Maximum response of AZA for MS</th>
<th>Outcome (cause of death)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 (2018)</td>
<td>70/F</td>
<td>Therapy-related MDS (MDS-RS-MLD)</td>
<td>Multiple skin lesions (LC)</td>
<td>A cycle of AZA (75 mg/m²) — 6 cycles of biomodulatory therapy: AZA (75 mg/body × 7 days), pegylatizone and ATRA</td>
<td>7</td>
<td>Clinical resolution</td>
<td>Died (AML progression)</td>
<td>[13]</td>
</tr>
<tr>
<td>10 (present case)</td>
<td>89/M</td>
<td>MDS-EB-2</td>
<td>Skin</td>
<td>AZA (37.5 mg/m² × 7 days)</td>
<td>16</td>
<td>Clinical resolution</td>
<td>Died (AML progression)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

F: female; M: male; MS: myeloid sarcoma; CMML: chronic myelomonocytic leukemia; MDS: myelodysplastic syndrome; AML: acute myeloid leukemia; EB: excess blasts; AZA: azacitidine; RT: radiotherapy; Ara C: cytarabine; CAG: cytarabine, aclacinomycine, and granulocyte colony-stimulating factor (G-CSF); DNR: daunorubicin; FDG: fluorodeoxyglucose; PET-CT: positron emission tomography-computed tomography; N/A: not available; LC: leukemia cutis; MLD: multilineage dysplasia; IDR: idarubicin; allo-HSCT: allogeneic hematopoietic stem-cell transplantation; CLAG: cladribine, high-dose cytarabine, and G-CSF; DLI: donor lymphocyte infusion; FLAG: fludarabine, high-dose cytarabine, and G-CSF; GO: gemtuzumab ozogamicin; 6-MP: 6-mercaptopurine; MDS-RS: MDS with ringsideroblasts; ATRA: all-trans-retinoic acid. **Ongoing.
needed, treatment with AZA should be considered as a potential treatment strategy when MS develops in patients with myeloid malignancies, such as MDS, especially elderly patients who are ineligible for intensive treatment. If an effect on MS is confirmed in such cases, AZA treatment should be continued as much as possible.

Data Availability
The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval
The authors declare that this work was performed with all due respect to the code of ethics.

Consent
Written informed consent was obtained from the family of the patient for publication of this case report and any accompanying images.

Conflicts of Interest
The authors declare no conflicts of interest in association with the present study.

References
