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CASE REPORT

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Successful management of therapy-related chronic myelomonocytic leukemia with cytarabine, aclarubicin, and azacitidine following tegafur/gimeracil/oteracil

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Abstract

A 55-year-old man was diagnosed with therapy-related chronic myelomonocytic leukemia (t-CMML) after exposure to tegafur/gimeracil/oteracil. Although he was refractory to hydroxyurea and low-dose cytarabine, combination therapy with cytarabine, aclarubicin and azacitidine (CA-AZA) provided good disease control, and he underwent allogeneic stem cell transplantation. This report has two key massages. First, tegafur/gimeracil/oteracil may have a potential risk of developing t-CMML. Second, CA-AZA therapy may be considered as a therapeutic option for patients with t-CMML.

KEYWORDS

azacitidine, CA-AZA, chronic myelomonocytic leukemia, tegafur, therapy related

1 | INTRODUCTION

According to World Health Organization (WHO) classification, chronic myelomonocytic leukemia (CMML) is defined as a clonal hematopoietic malignancy with features of both myeloproliferative neoplasm (MPN) and myelodysplastic syndrome (MDS). A variety of treatments were administered for CMML, but the treatment response was limited.[1] Poor chemotherapy response induced poor prognosis, especially in high-risk patients.[1]

Therapy-related CMML (t-CMML) is one of the phenotypes of therapy-related myeloid neoplasms (t-MN). T-CMML is a rare disease with an approximate frequency of 10% of CMML.[2,3] Patients with t-CMML are reported to have a poorer chemotherapy response and prognosis compared with those with de novo CMML, and there is no standard approach to treatment of t-CMML.[2,3] Here in, we presented a t-CMML case who was successfully managed with cytarabine, aclarubicin, and azacitidine therapy (CA-AZA) and cord blood transplantation (CBT).

2 | CASE PRESENTATION

A 55-year-old man presented to our hospital with osteocopic pain, fever, and erythema. Three years ago, he had an operation on pancreatic cancer without elevating preoperative CEA, DUPAN-1, or SPan-1. He received postoperative

chemotherapy, tegafur/gimeracil/oteracil, for 8 months. He did not receive any other medications and did not have any allergies.

His vital signs were as follows: body temperature was 38.2°C, blood pressure was 117/68 mm Hg, heart rate was 92/min, respiratory rate was 16/min, and SpO_2 was 94% in ambient air. Physical examination showed scattered erythema in his body and upper and lower extremities. There was no juvenile distension and edema of lower extremity. Heart sounds were of a normal rhythm, and there was no murmur. Laboratory findings were as follows: white blood cells of 48 400/μL (5% of blastoid cells with Auer rods; existence of hypersegmented neutrophils), red blood cell of 331×10^4/μL, hemoglobin of 10.5 g/dL, mean cell volume of 99 fL, platelet count of 4.9×10^4/μL, lactate dehydrogenase of 1730 international units (IU)/L, C-reactive protein of 3.32 mg/dL, blood urea nitrogen of 12 mg/dL, creatinine of 0.83 mg/dL, aspartate aminotransferase of 56 IU/L, alanine aminotransferase 16 IU/L, alkaline phosphatase of 350 IU/L, prothrombin time/international normalized ratio of 1.14, fibrinogen of 591 mg/dL, and fibrin/fibrinogen degradation products of 220 μg/mL. CEA was 5.1 ng/mL, DUPAN-2 was undetectable, and SPan-1 was 12.6 U/mL. Bone marrow aspiration showed that total cell count was 125 000 cells/μL, monocytes were 8.0%, and blastoid cell was 2.6% with Auer rods. Flow cytometric immunophenotyping study revealed a positive test for CD13, CD33, and CD56. Bone marrow biopsy showed an increase of monocytes and no fibrosis. Chromosomal analysis by the G-banding method showed t (11; 19). There were no other diagnostic genetic abnormalities, such as JAK2 and CALR mutation. Whole-body CT showed no hepatomegaly, splenomegaly, or lymphadenopathy. We performed a skin biopsy for erythema, and the histology showed neutrophilic dermatosis. The patient was diagnosed with CMML (WHO: CMML-2, FAB: MPN-CMML) and Sweet's syndrome (SS). CMML-specific prognostic score (CPSS) was four points, and it was considered as high risk.

We started the patient on 2000 mg/day of hydroxyurea (HU) followed by low-dose cytarabine (LD-AraC) of 10 mg/m^2 every 12 hours for 14 days, but the disease was progressing. We started CA-AZA therapy (IV aclarubicin, 14 mg/m^2 on days 1 and 2; IV azacitidine, 75 mg/m^2 on days 1-7, and SC cytarabine, 20 mg/m^2 on days 1-7). The patient achieved good disease control (Figure 1). According to MDS/MPN-International working group response criteria,[4] he achieved almost all criteria of CR except for osteomyelofibrosis after four cycles of CA-AZA. In addition, CPSS was improved one point, and the patient was considered "intermediate-1 risk." The patient was looking for a curable treatment. He had undergone CBT with myeloablative conditioning and achieved complete remission after CBT.

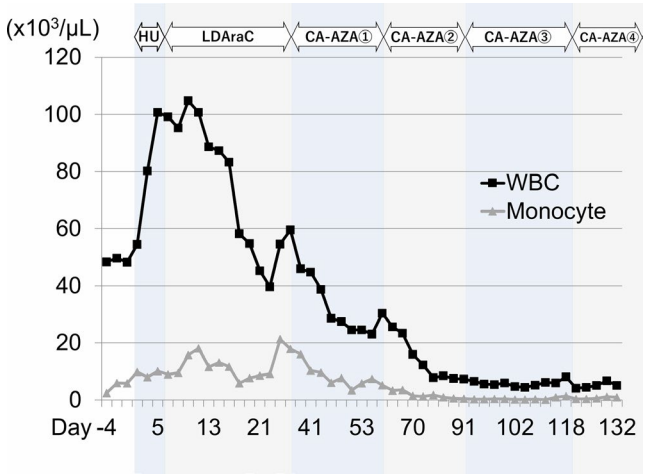

FIGURE 1 Clinical course after treatment. CA-AZA: cytarabine, aclarubicin, and azacitidine therapy; HU: hydroxyurea; LD-AraC: low-dose cytarabine; WBC: white blood cell count

3 | DISCUSSION

Prognosis of t-CMML was reported as poorer than that of de novo CMML. One retrospective study [2] showed that, in de novo CMML and t-CMML, median overall survival (OS) was 26 months and 10.9 months, respectively ($P < .0001$). Another study [3] reported median OS to be 13 months and 22 months, respectively ($P = .023$). These studies reported that high-risk cytogenetic abnormalities were more likely detected in t-CMML patients and may be related to poor prognosis. This differential prognosis is important to decide on the treatment strategy, so whether the diagnosis is t-CMML or not needs to be confirmed.

According to WHO classification, t-CMML is not defined as a separate disease entity and is one of the t-MN. Conventional therapies associated with t-MN are alkylating agents, radiation therapy, and topoisomeraseⅡ inhibitors. In t-CMML, it was reported that most of patients had prior exposure to these therapies.[2] Our patient had not used the aforementioned drugs but did use tegafur/gimeracil/oteracil, which are antimetabolites, as a postoperative therapy for pancreatic cancer before CMML developed. On administering tegafur,[5] tegafur/uracil,[5,6] and tegafur/gimeracil/oteracil,[7,8] patients were reported to have a potential risk of developing myeloid neoplasms. The Table 1 shows previously reported patients with t-MN following tegafur. Median age at diagnosis of t-MN was 67 years old, and median time of tegafur usage was 24 months. Median onset time from initial therapy was 3 years. However, these reports did not include t-CMML cases. Our report suggests that on administering tegafur combined with other drugs, the patients had a risk of developing t-CMML. This information is important because t-CMML has a poor prognosis and this aids in early diagnosis.

Some treatment strategies for CMML were reported, but the treatment outcome was limited. On administering

TABLE 1 Therapy-related myeloid neoplasms after antimetabolites therapy

No	Age	Sex	t-MN	Proceed cancer	Tegafur combined drugs	Duration	Time from initial therapy	Reference
1	66	M	AML (M2)	Tongue/lung	Tegafur/uracil	24 mo	3 y	5
2	67	M	AML (M2)	Colon	Tegafur/uracil	7 mo	9 y	5
3	67	M	AML (M2)	Colon/rectum	Tegafur	90 mo	8 y	5
4	81	M	AML (M4)	Colon	Tegafur/uracil	24 mo	2 y	6
5	55	F	CML	Stomach	Tegafur/gimeracil/ oteracil	21 mo	3 y	7
6	78	M	CML	Stomach	Tegafur/gimeracil/ oteracil	30 mo	Receiving	8
7	55	M	CMML	Pancreas	Tegafur/gimeracil/ oteracil	8 mo	2.5 y	Our case

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; F, female; M, male; NA, no available data; t-MN, therapy-related myeloid neoplasms.

AZA monotherapy to patients with CMML was reported, response rate was 40%–50%, and complete remission (CR) rates were <20%.[1] Intensive chemotherapy achieved higher CR rates but caused more significant toxicities rather than low-dose chemotherapy.[9] There was no prospective study about t-CMML therapy, but, in some retrospective studies, it was treated the same as de novo CMML. One report showed that 11 t-CMML patients were treated with hypomethylating agents, such as azacitidine or decitabine, and no patients achieved CR.[2] The other reported that all 36 t-CMML patients who treated with the best supportive care, cytoreductive therapy, hypomethylating agents, AML like therapy, and immunomodulatory drugs/tyrosine kinase inhibitors died within 5 years.[3] These studies suggest that conventional MDS or CMML-like treatments including AZA monotherapy may be insufficient to control the disease of t-CMML.

Cytarabine, aclarubicin, and azacitidine therapy had a good response and mild toxicity for MDS/CMML. Compared with AZA monotherapy, CA-AZA had better overall response rate (ORR), longer OS, and similar toxicity (ORR: 17% for AZA versus 65% for CA-AZA; median OS: 7.9 months for AZA versus 11.1 months for CA-AZA; $P = .0167$).[10,11] Moreover, an animal study showed that cytarabine and azacitidine had a synergistic effect on leukemic cell death.[12] Thus, this combination was expected to have good antitumor effects. Our patient, who was diagnosed with t-CMML, had a good response to CA-AZA therapy, and this suggested the potential impact of CA-AZA in patients with t-CMML.

Allogeneic stem cell transplantation (SCT) is the only curable treatment for patients with CMML. In CMML, response rates and nonrelapse mortality after allogeneic SCT were reported to be 17%–50% and 12%–52%, respectively.[1] Additionally, some retrospective studies reported a variety of factors as predictors of OS after allogeneic SCT for patients with CMML, for example, complete remission, good performance status, and improvement of CPSS score just before allogeneic SCT and within 12 months of transplantation after diagnosis on multivariate analysis.[13-15] In our patient, CA-AZA therapy provided a rapid response, an improvement of CPSS, and achievement of almost all CR criteria with keeping performance status, which enabled the patient to undergo allogeneic SCT 5 months after the initial diagnosis. However, there is no report to evaluate how effective allogeneic SCT is for t-CMML and what factors predict the prognosis after SCT.

4 | CONCLUSION

This report has two key aspects of t-CMML for hematologists. One is that patients who received tegafur/gimeracil/oteracil could be exposed to risk of developing t-CMML as well as the other hematological neoplasms. This is important finding to distinguish t-CMML from de novo CMML. The other is that even though HU and LD-AraC had been noneffective in our patient, CA-AZA therapy provided a rapid response with keeping good performance status. CA-AZA therapy can be used in t-CMML patients not only as a salvage therapy, but also a pretransplant therapy. Since t-CMML had a poor prognosis, further studies and treatment strategies are necessary to improve the prognosis.

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CONFLICT OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS
SN, TT, and HI: contributed to the clinical data collection. SN: wrote the main manuscript. TT: checked and revised the

main manuscript. All authors read and approved the final manuscript.

ETHICAL APPROVAL

Written informed consent for publication of this information was obtained from the patient.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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