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Case Report

Sequential Combination of FLAM and Venetoclax plus Azacitidine to Bridge to Cord Blood Transplantation in a Patient with Primary Induction Failure Acute Myeloid Leukemia

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Azacitidine · Venetoclax · Refractory acute myeloid leukemia · Transplant · B-cell lymphoma-2

Abstract
Venetoclax (VEN) is an oral B-cell lymphoma-2 (BCL-2) inhibitor that has been widely used to treat various hematological disorders. Recent studies have demonstrated that VEN in combination with fludarabine-enhanced high-dose cytarabine (FLA) is effective for treating relapsed or refractory acute myeloid leukemia (AML). In the combination therapy, salvage chemotherapy and VEN are basically concurrently administrated; however, further optimization may enable the treatment to apply to larger numbers of patients with various clinical backgrounds. Here, we describe a case of refractory AML treated with a sequential combination of the intensive chemotherapy (fludarabine, cytarabine, and mitoxantrone; FLAM) and VEN/AZA to bridge to an unrelated cord blood transplantation (uCBT). By continuously adding VEN/AZA after FLAM, the patient achieved morphologic leukemia free state with only minor toxicities. Blood cell counts did not recover until the time of transplantation because of the deep myelosuppression caused by the treatment sequence, but the infection risk was safely managed during this period. After engraftment, maintenance therapy with VEN/AZA was performed, and the patient has survived without disease recurrence for over 9 months after transplantation. Our case suggests

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that bridging therapy with VEN and AZA from the time of the last chemotherapy to allogeneic transplantation may provide an effective and tolerable treatment strategy for refractory AML. Further studies of larger numbers of cases are needed to validate the effectiveness of this treatment.

Introduction

The prognosis of patients with chemotherapy-refractory or primary induction failure acute myeloid leukemia (AML) is poor; thus, new treatment strategies must be developed. Venetoclax (VEN) is an oral B-cell lymphoma-2 (BCL-2) inhibitor that has been widely used to treat various hematological disorders. VEN has also been used in combination with azacitidine (AZA) as a hypomethylating agent to treat AML, as reported in several clinical trials [1, 2]. Recent clinical studies showed that the combination of VEN and conventional intensive chemotherapy had promising effects in patients with AML who were chemotherapy-refractory or showed primary induction failure [3]. These studies demonstrated the safety and efficacy of VEN-containing combination chemotherapy. Basically, in these studies, the intensive chemotherapy and VEN were administrated in the same period; however, further optimization may enable treatment of larger numbers of patients with various clinical backgrounds. Herein, we report the successful clinical course used for a patient with AML showing primary induction failure involving a sequential combination of the intensive chemotherapy (fludarabine, cytarabine, and mitoxantrone; FLAM) and VEN/AZA. This treatment strategy enabled to enhance anti-tumor effect with decentralizing each adverse effect and was effective for bridging of unrelated cord blood transplantation (uCBT).

Case Report

A 44-year-old woman with chemotherapy-refractory AML, who had been diagnosed 2 months prior, presented to our hospital for further treatment. Her previous treatments included one course of idarubicin (IDA) and cytarabine (AraC) and one course of mitoxantrone, etoposide, and a high dose of cytarabine (HDAC). However, the disease was completely refractory to both treatments (Fig. 1). On admission to our hospital, she had a high fever, and her Eastern Cooperative Oncology Group performance status was 2. Blood tests showed a white blood cell count of 6,400/μL (blast: 95%) and a high WT-1 mRNA level of 100,000 copies/μg RNA. Her bone marrow was normocellular with a nucleated cell count of 32,000/μL and was occupied by more than 90% myeloperoxidase-positive blasts. The AML type was M1 according to French-American-British criteria. Immunostaining revealed high expression levels of BCL-2 in the AML blasts. Flow cytometry analysis showed that cytoplasmic MPO, CD13, CD33, CD34, HLA-DR, CD7, and CD38 were expressed in the AML blasts, whereas CD2, CD3, CD5, CD14, CD41, and CD61 were not. Moreover, FLT3-ITD/TKD and NPM1 mutations, major-BCR, and minor-BCR, PML-RARA, AML1-MTG8, CBFβMYH11, DEK-CAN, NUP98HOXA9, ETV6-AML1, E2A-PBX1, MLL-AF4, MLL-AF6, MLL-AF9, and MLL-ENL were not observed. A complex karyotype was observed in the G-band test. FLAM consisting of fludarabine (30 mg/m^2/day, days 1–5), a high dose of cytarabine (1,500 mg/m^2 twice daily, days 1–5), and mitoxantrone (15 mg/m^2/day, days 1–3) was administered as a salvage treatment, which reduced the number of blasts to 50% in the peripheral blood on day 9. Subsequently, VEN (200 mg/day once daily for 14 days) and AZA (75 mg/m^2/day, intravenously for 7 days) were started from day 10 of FLAM.

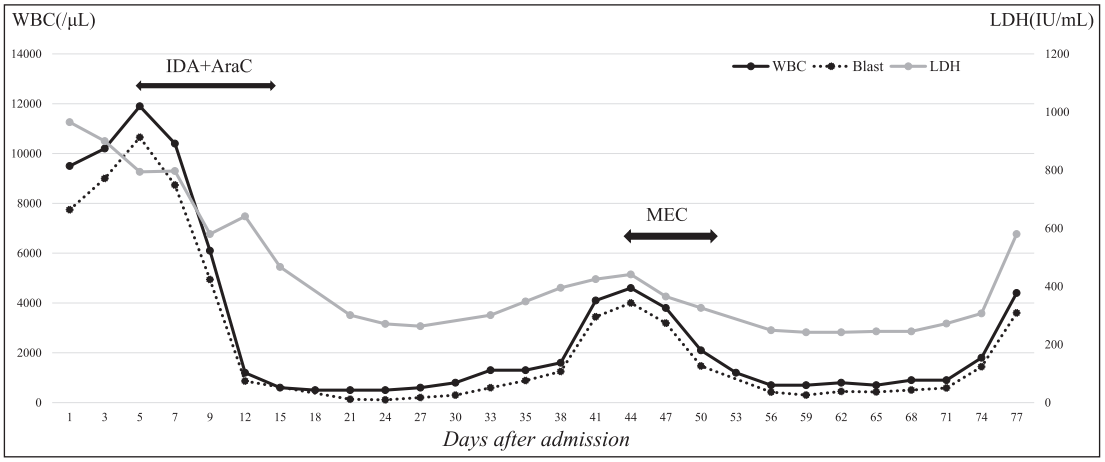

Fig. 1. Clinical course at the previous hospital. At diagnosis, BMA showed NCC was 320,00/μL, Blast rate was 75.0%, and chromosomal karyotype was complex at G-band test (20/20). WT-1 mRNA in the peripheral blood was 90,000copies/μg RNA. On day 44 after IDA + AraC, BMA showed NCC was 35,000/μL, Blast rate was 73.2%, and chromosomal karyotype was complex at G-band test (20/20). WT-1 mRNA in the peripheral blood was 86,000 copies/μgRNA. IDA, idarubicin; AraC, cytarabine; MEC, mitoxantrone/etoposide/cytarabine; BMA, bone marrow analysis; NCC, nucleated cell count; WT-1, Wilms tumor-1.

Expected adverse hematological events such as grade 4 neutropenia and thrombocytopenia were observed, but non-hematological severe adverse events were not observed during FLAM + AZA + VEN. The AML blasts were not detected in the peripheral blood after 4 days of VEN; the patient's bone marrow showed no morphological evidence of leukemia after 14 days of VEN. Minimal residual disease was not detected using flow cytometry. This enabled bridging allogeneic hematopoietic stem cell transplantation as a treatment strategy for AML; thus, on day 24 of FLAM, we started pretransplant conditioning with fludarabine (30 mg/m^2/day, days −7 to −2), busulfan (3.2 mg/kg/day, days −7 to −4), and melphalan (40 mg/m^2/day, days −3 to −2), and uCBT was performed (HLA 4/6 antigens matched, total nucleated cell count of 2.1 × 10^7/kg, and CD34-positive cell count of 0.85 × 10^5/kg). Tacrolimus (day 1, continuous concentration: 10–15 ng/mL) and mycophenolate mofetil (day 1,2000 mg/day orally) were administered as prophylaxis for acute graft-versus-host disease. Letermovir (480 mg/day, orally) was administered as a prophylaxis for cytomegalovirus on days 0 to +100. Granulocyte colony-stimulating factor support was started on day +5. Neutrophil engraftment was achieved on day 22 of uCBT. On day 28, complete remission (CR) was achieved, and WT-1 mRNA was normalized (<50 copies/μg RNA). Minimal residual disease was not detected using flow cytometry. We started reducing the tacrolimus and mycophenolate mofetil doses on day 30 and stopped these drugs by day 60. VEN maintenance therapy was started at 100 mg on day 40 and was increased to 400 mg in 100-mg increments every 3 days (400 mg dose of VEN was allowed in combination with L-AMB). We also resumed AZA therapy on day 74 after transplantation at 20 mg/m^2 for 3 days every 28 days and then continued VEN maintenance therapy. On day 80, VEN was reduced to 200 mg/day because L-AMB was changed to posaconazole. After a week, VEN was reduced to 50 mg/day to avoid severe cytopenia. After reducing the dose of VEN, any severe grade of cytopenia was not observed, and VEN was continued at the same dose. During the 2nd cycle of AZA (on day 108), we increased the dose of AZA to 75 mg/m^2 for 5 days. Because of reactivation of cytomegalovirus following discontinuation of letermovir, we postponed the 3rd cycle of AZA therapy, which was resumed on day +180. Graft-versus-host disease and other severe complications were not observed, and the patient is alive without relapse of AML at day +180. All clinical courses provided at our hospital are shown in Figure 2.

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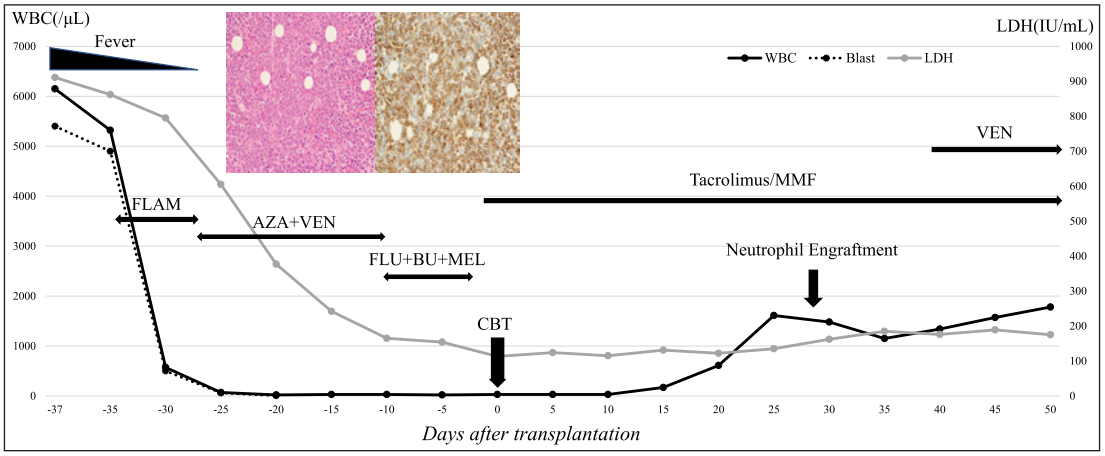

Fig. 2. Clinical course at our hospital. On admission, BMA showed NCC was 300,00/μL, blast rate was 93.8% and chromosomal karyotype was complex at G-band test (20/20). WT-1 mRNA in the peripheral blood was 100,000copies/μgRNA. Pathological images (×200 magnification) of hematoxylin and eosin staining (left) and BCL-2 staining (right) of bone marrow clot section at admission to our hospital. On day 10 before CBT, BMA showed NCC was 100/μL, Blast rate was 0% and chromosomal karyotype was 46, XX at G-band test (20/20). On day 28 after CBT, BMA showed NCC was 9,000/μL, Blast rate was 0% and chromosomal karyotype was 46, XY at G-band test (20/20). WT-1 mRNA in the peripheral blood was <50copies/μg RNA. FLAM, fludarabine/high-dose cytarabine/mitoxantrone: AZA, azacitidine: VEN, venetoclax: FLU + BU + MEL, fludarabine + busulfan + melphalan: CBT, cord blood transplant: MMF, mycophenolate mofetil BMA, bone marrow analysis: NCC, nucleated cell count: WT-1, Wilms tumor-1.

Discussion

The efficacy of combined VEN and intensive chemotherapy for relapsed/refractory AML has been widely studied. Shahswar et al. [3] reported the efficacy of salvage regimen FLA-IDA (fludarabine, cytarabine, and idarubicin) combined with 7 days of VEN in patients with relapsed/refractory AML. This regimen was well-tolerated, and patients showed a high overall response rate of 69% CR/CR with incomplete blood recovery (CRi). Hematopoietic stem cell transplantation was performed in patients who achieved a CR/CRi, resulting in an estimated 6-month overall survival and relapse-free survival rate of 76% [3]. DiNardo et al. [4] reported favorable results for FLAG-IDA combined with 14 days of VEN. In this study, this treatment led to a high overall response rate of 72% (n = 28/39) in relapsed/refractory AML, and 46% (n = 18/39) of patients underwent allotransplantation. The 1-year posttransplant survival rate was 78%. These studies suggest that FLA can be used as a basic regimen in combination with VEN and chemotherapy for refractory AML. In our case, we selected mitoxantrone rather than IDA as an anthracycline in combination with FLA because the patient was refractory to IDA and AraC, which were used as the first remission-induction therapy [5]. Moreover, we added AZA to FLAM + VEN before transplantation and resumed AZA/VEN as a posttransplant maintenance therapy. Clinical trials involving posttransplant use of AZA/VEN are currently underway and favorable results are awaited (Viale-T study, NCT04161885).

Our treatment regimen consisting of FLAM + AZA/VEN is similar to FLAM + amsacrine (FLAMSA), which has been used for refractory AML. FLAMSA is composed of three parts as follows: (1) induction therapy, (2) reduced intensity conditioning after 3 days of induction therapy, and (3) allogeneic immune response consisting of the graft-versus-leukemic effect and donor lymphocyte infusion [6]. In both therapies (FLAM + AZA/VEN and FLAMSA), transplantation can be performed without waiting for recovery of the blood cell count. In contrast

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to FLAMSA, VEN/AZA was added as a bridge from the last chemotherapy until allogeneic transplantation in FLAM + AZA/VEN. Since hematopoiesis can be rescued by upfront HSCT, it was possible to administer sufficient doses of VEN/AZA even though they caused deep myelosuppression. This administration appeared to result in a potent anti-tumor effect, and the patient went into morphologic leukemia free state. In addition, as the period from FLAM to transplant was sufficient, a myeloablative conditioning regimen could be used for CBT. This may be a different point from FLAMSA in which non-myeloablative conditioning regimens are used after concurrent combination with FLAM and amsacrine. It depends on the condition of each patient which conditioning intensity is better; however, especially for cord blood transplants like the presented case, the benefits of using myeloablative conditioning may be significant.

On the other hand, the therapeutic strategy could increase serious infection based on prolonged bone marrow suppression. In fact, previous studies reported that VEN combined with FLAG-IDA was associated with deep myelosuppression and infections, especially after the 2nd course [7]. Thus, in the combination with chemotherapy and VEN, very careful supportive therapies including the prophylactic use of antimicrobial agents and the frequent surveillance for infectious complications are essential for optimal patient care. Also, the patient population for which such intensive combination therapies are indicated should be carefully considered, and the chemotherapeutic partner of the AZA/VEN combination should be further optimized.

In conclusion, therapeutic modification in the combination of VEN and FLA should be considered on a patient-by-patient basis. FLAM + AZA/VEN was effective and well-tolerated in our patient, suggesting that bridging therapy with AZA/VEN from the last intensive chemotherapy to allogeneic transplantation is an effective and tolerable treatment strategy for refractory AML. As we only report a single case, our findings should be validated in future investigations, which may lead to the development of an efficient combination therapy for refractory AML.

Acknowledgments

We would thank our patient and all staff involved in this paper.

Statement of Ethics

This study was performed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects. Ethical approval is not required for this study in accordance with national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Hiroyuki Murakami treated the patient and wrote the paper. Tomohiro Toji and Tadashi Yoshino performed pathological analysis. Takeru Asano, Takashi Moriyama, Akifumi Matsumura, Hideaki Fujiwara, Noboru Asada, Daisuke Ennishi, Hisakazu Nishimori, Keiko Fuji, Nobuharu Fuji, and Yoshinobu Maeda worked to treat the patient. Ken-ichi Matsuoka designed and edited the paper.

Data Availability Statement

All data that support the findings of this study are included in this article. Further inquiries can be directed to the corresponding author.

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