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Case Report

Venetoclax-Azacitidine Bridging PTCy-haplo-PBSCT for Refractory Acute Myeloid Leukemia with *IDH2* Mutations

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Keywords
Acute myeloid leukemia · Venetoclax-azacitidine · PTCy-haplo-PBSCT · *IDH2* mutation

Abstract
Venetoclax and azacitidine combination therapy (VEN+AZA) is a promising novel therapy for elderly or unfit patients with acute myeloid leukemia (AML). Recently, VEN+AZA with subsequent allo-hematopoietic stem cell transplantation has been reported, and human leukocyte antigen-haploidentical peripheral blood stem cell transplantation using posttransplant cyclophosphamide (PTCy-haplo-PBSCT) from related donors appears to be a suitable option. Here, we report two elderly patients with refractory AML harboring an *IDH2* mutation, who were successfully treated with VEN+AZA bridged to PTCy-haplo-PBSCT. This report suggests the efficacy and safety of VEN+AZA as a bridging treatment for PTCy-haplo-PBSCT in refractory AML.

Introduction

Venetoclax and azacitidine combination therapy (VEN+AZA) is a promising novel therapy for elderly or unfit patients with acute myeloid leukemia (AML), owing to its excellent response and tolerability [1, 2]. Recently, VEN+AZA and subsequent allo-hematopoietic stem

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cell transplantation (allo-HSCT) have emerged as a superior treatment, rather than VEN+AZA maintenance alone, owing to a superior outcome in patients and good tolerability for elderly and fragile patients [3, 4]. However, the duration of response achieved by VEN+AZA is relatively short, and it is crucial to promptly find donor sources for patients who receive VEN+AZA as a bridging treatment to allo-HSCT. Owing to ease of accessibility to donor sources and good tolerability of transplantation, human leukocyte antigen (HLA)-haploidentical peripheral blood stem cell transplantation using posttransplant cyclophosphamide (PTCy-haplo-PBSCT) from related donors was chosen as a suitable treatment in this instance. Here, we report two elderly patients with refractory AML harboring an *IDH2* mutation, who were successfully treated with VEN+AZA bridging PTCy-haplo-PBSCT.

Case Report

Case 1

A 69-year-old female, who had received adjuvant chemotherapy for myxofibrosarcoma of the right femur 7 years ago, was diagnosed with therapy-related AML. Genetic analysis of the bone marrow (BM), using next-generation sequencing (NGS), revealed that the tumor clone harbored *IDH2*^{R140Q}, *NRAS*, and *KRAS* mutations (Table 1). Daunorubicin and cytarabine combination therapy (DNR+Ara-C) was initiated as induction therapy. Unfortunately, the patient developed severe pneumonia on day 2, and induction therapy was suspended on the same day. Antibiotic therapy with methylprednisolone pulse followed by steroid therapy was initiated. Although she recovered from severe pneumonia, normal hematopoiesis did not recover, and bone marrow aspiration revealed that 44% of the BM cells were myeloblasts. Therefore, we decided to start VEN+AZA as a salvage chemotherapy. Although grade 4 leukopenia and neutropenia were prolonged for about 3 weeks, normal hematopoiesis gradually recovered, and non-hematological toxicity was tolerable by VEN+AZA. After one cycle of VEN+AZA treatment, hematological complete remission (CR) was achieved. Another cycle of VEN+AZA and one cycle of azacitidine monotherapy were added, and subsequently, she received PTCy-haplo-PBSCT from a related donor who was HLA 4/8 matched. Fludarabine 30 mg/m^2 and busulfan 3.2 mg/kg were administered for 5 days and 2 days, respectively, and 4 Gy of total body irradiation was administered as reduced-intensity conditioning. Posttransplantation cyclophosphamide levels were 40 mg/kg on day 3 and day 4, and tacrolimus and mycophenolate mofetil (TAC+MMF) was started on day 5 as graft-versus-host disease (GVHD) prevention. Engraftment was performed smoothly on day 17, and no acute GVHD appeared after engraftment. The patient's clinical course after transplantation was uneventful, and she was discharged on day 47. The clinical course from the start of VEN+AZA treatment to transplantation is shown in Figure 1. It also shows the levels of Wilms tumor 1 (*WT1*) mRNA in peripheral blood (PB) and variant allele frequency (VAF) of *IDH2*^{R140Q} mutation in the BM. In this case, *WT1* mRNA of PB on day 30 after transplantation was <50 copies/μg RNA, and hematological CR was maintained on day 180 after transplant. Unfortunately, the patient died on day 193 due to thrombotic microangiopathy.

Case 2

A 62-year-old male was diagnosed with AML with intermediate risk, according to the ELN 2017 classification [5], indicating that the tumor clones harbored *IDH2*^{R172K}, *DNMT3A*, *BCOR*, and *BCORL1* mutations (Table 2). DNR+Ara-C was initiated as induction therapy, during which he developed a skin infection of *Stenotrophomonas maltophilia* and recovered after administration of sulfamethoxazole/trimethoprim. Unfortunately, normal hematopoiesis did not

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Table 1. Laboratory data and findings of bone marrow aspiration of case 1 on the first visiting day

CBC and coagulation test	Biochemistry	BMA findings and others
WBC 7,910/μL	TP 6.7 g/dL	NCC 22,000/μL
Mybl 94%	Alb 4.9 g/dL	Megakaryocyte 12/μL
Neu 0%	T.Bil 0.5 mg/dL	Mybl 78.2%
Mo 0%	AST 15 U/L	Flow cytometry: blast gating
Lymph 5%	ALT 15 U/L	CD13+, CD33+, CD34+, HLA-DR+, MPO+, CD38+, CD117+
RBC 2.33 × 10^6/μL	LDH 364 U/L	Chromosome analysis:
MCV 94.4 fL	γ-GTP 37 U/L	46, X, inv(X) (p11. 4q25) [20/20]
Hb 7.5 g/dL	UA 4.5 mg/dL	Others: PB: *WT1* mRNA 42,000 copies/μg RNA
Reti 0.3%	Cre 1.09 mg/dL	Genetic analysis of BM: *IDH2*^{R140Q} mutation (VAF) 0.398
Plt 4.3 × 10^4/μL	BUN 16 mg/dL	*NRAS* mutation (VAF) 0.179
APTT 34.6 s	Na 140 mmol/L	*KRAS* mutation (VAF) 0.215
PT (%) 62%	K 4.1 mmol/L	
Fib 423 mg/dL	Cl 104 mmol/L	
D-D 1.6 μg/mL	Ca 9.0 mg/dL	
FDP 3.2 μg/mL	IP 3.4 mg/dL	

CBC, complete blood count; WBC, white blood cell; Mybl, myeloblast; Neu, neutrophil; Mo, monocyte; Lymph, lymphocyte; RBC, red blood cell; MCV, mean corpuscular volume; Hb, hemoglobin; Reti, reticulocyte; Plt, platelet; APTT, activated partial thromboplastin time; PT, prothrombin time; Fib, fibrinogen; D-D, D-dimer; FDP, fibrin and fibrinogen degradation products; TP, total protein; Alb, albumin; T.Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; γ-GTP, γ-glutamyl transpeptidase; UA, uric acid; Cre, creatinine; BUN, blood urea nitrogen; Na, sodium; K, potassium; Cl, chlorine; Ca, calcium; IP, inorganic phosphorus; BMA, bone marrow aspiration; NCC, nucleated cell count; CD, cluster of differentiation; HLA, human leukocyte antigen; MPO, myeloperoxidase; PB, peripheral blood; BM, bone marrow; *WT1*, Wilms tumor 1; VAF, variant allele frequency.

recover, and bone marrow aspiration on day 28 revealed that 29% of BM cells were myeloblasts. Therefore, we decided to start VEN+AZA as a salvage chemotherapy. Although grade 4 leukopenia and neutropenia were prolonged for about 4 weeks, normal hematopoiesis gradually recovered, and non-hematological toxicity was tolerable by VEN+AZA. After one cycle of VEN+AZA treatment, hematological CR was achieved. An additional cycle of VEN+AZA was added, and the patient subsequently received PTCy-haplo-PBSCT from a related donor who was HLA 4/8 matched. Fludarabine 30 mg/m^2 and busulfan 3.2 mg/kg were administered for 5 days and 2 days, respectively, and 4 Gy total body irradiation was administered as reduced-intensity conditioning. Posttransplantation cyclophosphamide was administered at 40 mg/kg on days 3 and 4, and TAC+MMF was initiated on day 5 for GVHD prevention. Engraftment was performed smoothly on day 14, and no acute GVHD appeared after engraftment. The patient's clinical course after transplantation was uneventful, and he was discharged on day 48. The clinical course from the start of VEN+AZA treatment to transplantation is presented in Figure 2. It also shows levels of *WT1* mRNA of PB and VAF of *IDH2*^{R172K} mutation of BM. In this case, *WT1* mRNA of PB on day 30 after transplantation was <50 copies/μg RNA, and hematological CR was maintained on day 360 after transplantation. One and a half years have passed since the transplant, and the patient is still alive without relapse.

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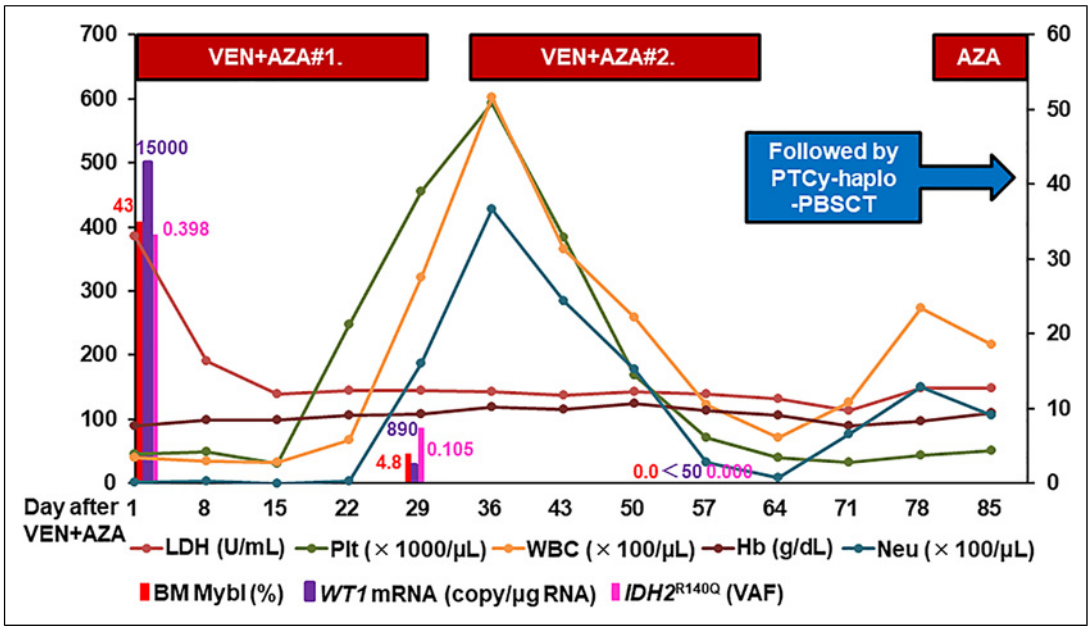

Fig. 1. Clinical course of case 1, from the start of VEN+AZA treatment until transplantation. LDH and Plt follow the left axis, and WBC, Hb, and Neu follow the right axis. Myeloblast percentage in BM, *WT1* mRNA in PB, and VAF of *IDH2*^{R140} mutation in BM are represented by vertical bars. VEN+AZA#1, first cycle of venetoclax and azacitidine combination therapy; VEN+AZA#2, second cycle of venetoclax and azacitidine combination therapy; AZA, azacitidine monotherapy; LDH, lactate dehydrogenase; Plt, platelet count; WBC, white blood cell count; Hb, hemoglobin; Neu, neutrophil count; PB, peripheral blood; BM, bone marrow; Mybl, myeloblast; *WT1*, Wilms tumor 1; VAF, variant allele frequency.

Discussion

The duration of response to VEN+AZA was relatively short if exclusively VEN+AZA was continued as maintenance therapy, and subsequent allo-HSCT using cord blood and a matched sibling donor for newly diagnosed AML patients older than 60 years was reported to be promising [4]. In contrast, PTCy-haplo-PBSCT has advantages, including donor source availability, high tolerability associated with early engraftment, and low incidence of severe acute GVHD among alternative donor sources. These properties seem suitable for subsequent allo-HSCT after VEN+AZA treatment, particularly in elderly AML patients. Notably, PTCy-haplo-PBSCT was promptly performed after bridging VEN+AZA therapy and showed good tolerability in elderly patients with AML. As mentioned above, cord blood is a reasonable alternative graft for post-VEN+AZA transplantation [4]; however, which graft is better remains undetermined.

Generally speaking, hematological toxicity of VEN+AZA is severe, and grade 4 leukopenia and neutropenia are often prolonged and immediate transplant after achievement of hematological CR seems to be a reasonable option to avoid additional risk. However, we needed time to prepare the donor for PB stem cell collection and we considered additional chemotherapy as consolidation therapy to prevent relapse. Then, we decided to administer one more cycle of VEN+AZA and one cycle of AZA in the case 1 and one more cycle of VEN+AZA in the case 2. On the other hand, maintenance therapy of *IDH2* inhibitor after transplantation has been studied as effective approach to prevent relapse [6], but *IDH2* inhibitor was not approved in Japan and we did not perform maintenance therapy by *IDH2* inhibitor.

Table 2. Laboratory data and findings of bone marrow aspiration of case 2 on the first visiting day

CBC and coagulation test	Biochemistry	BMA and other findings
WBC 1,170/μL	TP 7.8 g/dL	NCC 92,000/μL
Mybl 0%	Alb 4.7 g/dL	Megakaryocyte 49/μL
Neu 29%	T.Bil 0.7 mg/dL	Mybl 55.8%
Mo 3%	AST 26 U/L	Flow cytometry: blast gating
Lymph 67%	ALT 38 U/L	CD13+, CD33+, CD34+, HLA-DR+, MPO+, CD38+, CD117+
RBC 3.43 × 10^6/μL	LDH 169 U/L	Chromosome analysis: 46, XY [20/20]
MCV 109.0 fL	γ-GTP 46 U/L	Others: PB: *WT1* mRNA 3,300 copies/μg RNA
Hb 13.2 g/dL	UA 7.2 mg/dL	Genetic analysis of BM: *IDH2*^{R172K} mutation (VAF) 0.208
Reti 1.65%	Cre 1.05 mg/dL	*DNMT3A* mutation (VAF) 0.048
Plt 19.5 × 10^4/μL	BUN 16 mg/dL	*BCOR* mutation (VAF) 0.29
APTT 27.0 s	Na 140 mmol/L	*BCORL1* mutation (VAF) 0.057
PT (%) 117%	K 4.1 mmol/L	
Fib 288 mg/dL	Cl 105 mmol/L	
D-D 1.1 μg/mL	Ca 9.7 mg/dL	
FDP <2.5 μg/mL	IP 2.3 mg/dL	

CBC, complete blood count; WBC, white blood cell; Mybl, myeloblast; Neu, neutrophil; Mo, monocyte; Lymph, lymphocyte; RBC, red blood cell; MCV, mean corpuscular volume; Hb, hemoglobin; Reti, reticulocyte; Plt, platelet; APTT, activated partial thromboplastin time; PT, prothrombin time; Fib, fibrinogen; D-D, D-dimer; FDP, fibrin and fibrinogen degradation products; TP, total protein; Alb, albumin; T.Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; γ-GTP, γ-glutamyl transpeptidase; UA, uric acid; Cre, creatinine; BUN, blood urea nitrogen; Na, sodium; K, potassium; Cl, chlorine; Ca, calcium; IP, inorganic phosphorus; BMA, bone marrow aspiration; NCC, nucleated cell count; CD, cluster of differentiation; HLA, human leukocyte antigen; MPO, myeloperoxidase; PB, peripheral blood; BM, bone marrow; *WT1*, Wilms tumor 1; VAF, variant allele frequency.

However, both AML patients harboring *IDH2*^{R140Q} and *IDH2*^{R172K} mutations were refractory to conventional chemotherapy, although they showed good response with VEN+AZA. Recently, it was reported that *IDH1/2* mutations are favorable response markers for AML patients treated with VEN+AZA, with both *IDH2*^{R140} and *IDH2*^{R172} mutations presenting similar outcomes [7]. This study included patients with untreated AML patients with *IDH2* mutations, and VEN+AZA for the first-line chemotherapy was reasonable option, but genetics analysis using NGS took time to see results in our institute, and we selected conventional chemotherapy instead of waiting for the results of genetic analysis in both cases. On the other hand, genetic analysis revealed the *IDH2* mutations on the day when we selected salvage chemotherapy in both cases, and we considered possibility that AML patient with *IDH2* and *RAS* mutations in the case 1 might be refractory to VEN+AZA [8], but she was old and fragile and there was no effective and tolerable salvage regimen except VEN+AZA.

AML patients with *IDH1/2* mutations exhibited a longer duration of response to VEN+AZA than those without mutations [7]. However, the median duration of composite CR was reported as 29.5 months [7], and the benefit of allo-HSCT for AML patients with *IDH1/2* mutations has been confirmed [9], which seems to be necessary for patients who are eligible for allo-HSCT.

In our cases, *WT1* mRNA of PB and VAF of both *IDH2* mutations in the BM were correlated with the marrow blast ratio. Due to its low cost and availability, *WT1* mRNA of PB might be a more useful marker for treatment response to VEN+AZA than NGS of BM. Certainly, multiparametric flow

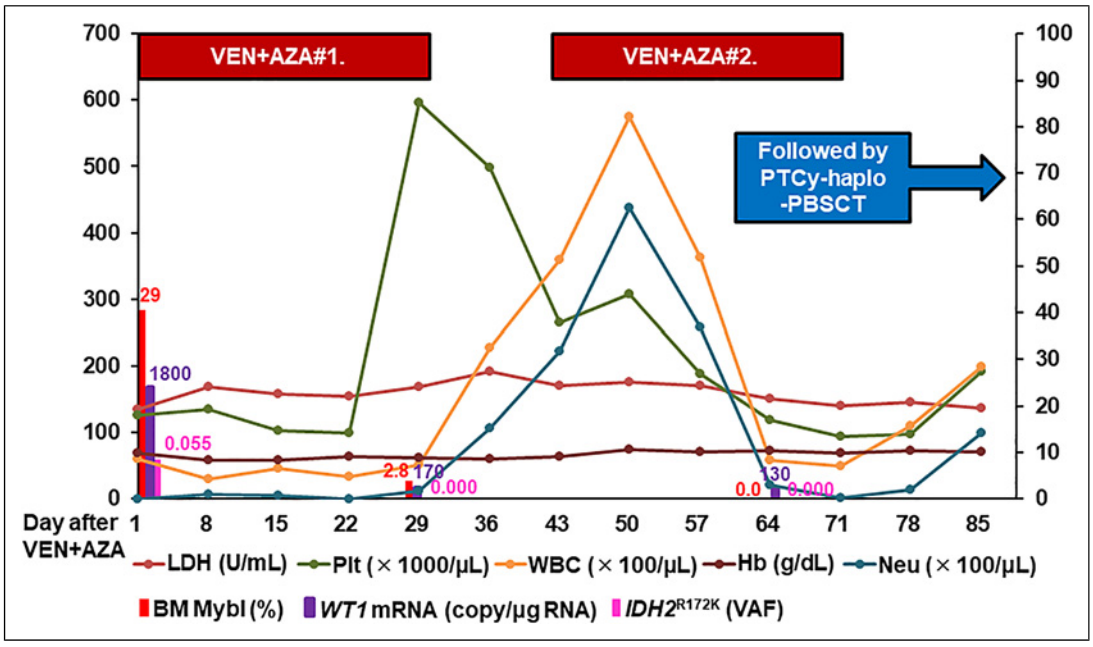

Fig. 2. Clinical course of case 2, from the start of VEN+AZA treatment until transplantation. LDH and Plt follow the left axis, and WBC, Hb, and Neu follow the right axis. Myeloblast percentage of BM, *WT1* mRNA of PB, and VAF of *IDH2*^{R172} mutation of BM are represented by vertical bars. VEN+AZA#1, first cycle of venetoclax and azacitidine combination therapy; VEN+AZA#2, second cycle of venetoclax and azacitidine combination therapy; LDH, lactate dehydrogenase; Plt, platelet count; WBC, white blood cell count; Hb, hemoglobin; Neu, neutrophil count; PB, peripheral blood; BM, bone marrow; Mybl, myeloblast; *WT1*, Wilms tumor 1; VAF, variant allele frequency.

cytometry was recommended to evaluate measurable residual disease [10], but multiparametric flow cytometry was not approved in Japan and we could not perform it to evaluate disease status. In addition, *WT1* mRNA levels of less than 50 copies/μg RNA on day 30 after transplant were reported as a possible positive prognostic factor for PTCy-haplo-PBSCT [11] and may also be useful for the assessment of disease status after transplantation in VEN+AZA bridging PTCy-haplo-PBSCT.

In conclusion, this report suggests the efficacy and safety of VEN+AZA as a bridging treatment for PTCy-haplo-PBSCT in elderly patients with refractory AML harboring *IDH2* mutations; however, this case report only included 2 cases with limited data; thus, further studies and evidence are warranted. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533749).

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Statement of Ethics

The authors certify that they have obtained all appropriate patient consent forms. Written informed consent for case 1 was obtained from the patient for publication of the details of their medical case and any accompanying images prior to their passing away. Written informed consent for case 2 was obtained from the patient for publication of the details of their medical case and any accompanying images. The completed consent form is available to the editor if requested and will be treated confidentially. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors declare no potential conflicts of interest regarding the publication of this study.

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Author Contributions

Y.D. and H.S. managed clinical practice and authored this report. T.I., T.K., S.O., N.N., T.M., and N.S. provided advice on this paper. Y.N. and S.O. provided data on genetic analysis using NGS and advised on the paper. M.T. supervised the clinical practice.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

References

1 DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med. 2020;383(7):617–29.
2 Gangat N, Tefferi A. Venetoclax-based chemotherapy in acute and chronic myeloid neoplasms: literature survey and practice points. Blood Cancer J. 2020;10(11):122.
3 Bazarbachi A. Exciting times ahead for older patients with acute myeloid leukemia: azacitidine and venetoclax followed by allogeneic hematopoietic cell transplantation. Bone Marrow Transplant. 2022;57(2):147–8.
4 Pollyea DA, Winters A, McMahon C, Schwartz M, Jordan CT, Rabinovitch R, et al. Venetoclax and azacitidine followed by allogeneic transplant results in excellent outcomes and may improve outcomes versus maintenance therapy among newly diagnosed AML patients older than 60. Bone Marrow Transplant. 2022;57(2):160–6.
5 Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424–47.
6 Fathi AT, Kim HT, Soiffer RJ, Levis MJ, Li S, Kim AS, et al. Enasidenib as maintenance following allogeneic hematopoietic cell transplantation for IDH2-mutated myeloid malignancies. Blood Adv. 2022;6(22):5857–65.
7 Pollyea DA, DiNardo CD, Arellano ML, Pigneux A, Fiedler W, Konopleva M, et al. Impact of venetoclax and azacitidine in treatment-naive patients with acute myeloid leukemia and *IDH1/2* mutations. Clin Cancer Res. 2022;28(13):2753–61.

Case Rep Oncol 2023;16:999–1006
DOI: 10.1159/000533749

8 DiNardo CD, Tiong IS, Quaglieri A, MacRaild S, Loghavi S, Brown FC, et al. Molecular patterns of response and treatment failure after frontline venetoclax combinations in older patients with AML. Blood. 2020;135(11):791–803.
9 Kunadt D, Stasik S, Metzeler KH, Röllig C, Schliemann C, Greif PA, et al. Study Alliance Leukemia (SAL). Impact of *IDH1* and *IDH2* mutational subgroups in AML patients after allogeneic stem cell transplantation. J Hematol Oncol. 2022;15(1):126.
10 Heuser M, Freeman SD, Ossenkoppele GJ, Buccisano F, Hourigan CS, Ngai LL, et al. 2021 Update on MRD in acute myeloid leukemia: a consensus document from the European LeukemiaNet MRD Working Party. Blood. 2021;138(26):2753–67.
11 Kitamura W, Fujii N, Nawa Y, Fujishita K, Sugiura H, Yoshioka T, et al. Possible prognostic impact of *WT1* mRNA expression at day +30 after haploidentical peripheral blood stem cell transplantation with posttransplant cyclophosphamide for patients with myeloid neoplasm: a multicenter study from the Okayama Hematological Study Group. Int J Hematol. 2022;115(4):515–24.