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T/myeloid mixed-phenotype acute leukemia treated with venetoclax and decitabine: A case report

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Abstract

BACKGROUND

Mixed-phenotype acute leukemia (MPAL) is characterized by acute undifferentiated leukemia with blasts co-expressing myeloid and lymphoid antigens. However, consensus regarding the ideal management strategy for MPAL is yet to be established, owing to its rarity.

CASE SUMMARY

A 55-year-old male was diagnosed with T/myeloid MPAL. Vincristine, prednisolone, daunorubicin, and L-asparaginase were administered as induction chemotherapy. Septic shock occurred 10 d after induction, and bone marrow examination following recovery from sepsis revealed refractory disease. Venetoclax and decitabine were administered as chemotherapy-free induction therapy to reduce the infection risk. There were no serious infections, including febrile neutropenia, at the end of the treatment. After receiving two additional cycles of venetoclax/decitabine, the patient underwent haploidentical peripheral blood stem-cell transplantation and achieved complete response (CR) to treatment.

CONCLUSION

CR was maintained in a patient with MPAL who underwent haploidentical peripheral blood stem-cell transplantation after additional venetoclax/decitabine cycles.

INTRODUCTION

The term "mixed-phenotype acute leukemia" (MPAL) refers to a heterogeneous group of uncommon acute leukemias accounting for ≤ 5% of all acute leukemias, characterized by co-expression of myeloid and lymphoid antigens on the same blasts or by the presence of two separate cell populations expressing various lineage traits[1]. In 2022, the World Health Organization (WHO) recognized T/myeloid MPAL as one of five MPAL subtypes of acute leukemia of uncertain lineage[2]. The prognosis and consequences of MPAL are worse than those of standard-risk acute myeloid leukemia (AML) or acute lymphocytic leukemia (ALL)[1]. The prognosis is exceedingly dismal for patients with relapsed/refractory (R/R) AML who are unsuitable candidates for intensive chemotherapy regimens or allogeneic hematopoietic stem-cell transplantation (allo-HSCT).

Given the rarity of MPAL, an ideal strategy for disease management is yet to be established. AML- and ALL-based regimens should be prospectively validated, given the inevitable bias inherent in retrospective studies and small case series. Currently, an ALL-like induction protocol is recommended, then allogeneic stem cell transplantation (allo-SCT) is performed after the initial complete remission. Moreover, the treatment strategy has not been well established since introducing the concept of MPAL. Salvage treatment for relapsed/refractory (R/R) acute leukemias of ambiguous lineage, not otherwise specified (ALAL-NOS), remains a major concern. Currently, allo-HSCT is the only treatment strategy for ALAL-NOS; however, the prognosis remains poor if complete response (CR) is not achieved before allo-HSCT[3]. Chemotherapy is ineffective for ALAL-NOS. Therefore, salvage treatments are required to enhance the CR before allo-HSCT.

To the best of our knowledge, the current report is the third instance of successful treatment with venetoclax and a hypomethylating agent (HMA) in a patient with

refractory T/myeloid MPAL. Future studies should examine the effectiveness of this approach.

CASE PRESENTATION

Chief complaints

A 55-year-old male patient with dizziness was admitted to the hospital.

History of present illness

Beginning one week prior, the patient developed dizziness and difficulty breathing when climbing stairs.

History of past illness

He had a history of hypertension and epilepsy and was taking levetiracetam.

Personal and family history

No specific findings were recorded.

Physical examination

There were no specific findings on palpation of the spleen, the face appeared markedly pale, and there were no bruises on the skin.

Laboratory examinations

Neutropenia ($1.12 \times 10^3/mm^3$), anemia (4.0 g/dL), and thrombocytopenia ($12 \times 10^3/mm^3$) were detected in peripheral blood. Figure 1 describes the findings of the bone marrow examination. Flow cytometry showed the expression of cMPO+, CD 13+, CD33+, CD64+, CD117+, CD34+, and high cytoplasmic CD3. Chromosomal karyotyping revealed a 48, XY, add(11)(q23), add(12)(p13).-20,-22,+4mar karyotype. Fluorescence *in situ* hybridization revealed KMT2A positivity. Next-generation sequencing results were negative for the BCR-ABL gene or other mutations.

Imaging examinations

No specific findings were observed on the chest X-ray.

FINAL DIAGNOSIS

A diagnosis of T/myeloid MPAL was confirmed by bone marrow aspiration, which was suggestive of acute leukemia.

TREATMENT

Vincristine, prednisolone, daunorubicin, and L-asparaginase (VPDL) were administered as induction therapy. Ten days after initiating induction chemotherapy, the patient developed septic shock with hypotension (blood pressure 80/40 mmHg) and high fever (39.2°C). Effective antibiotics (colistin, meropenem, and ciprofloxacin) were initiated after a blood culture-confirmed bacteremia caused by extended-spectrum beta-lactamase-positive *Klebsiella pneumoniae*. Bone marrow examination after recovery from sepsis revealed refractory disease, and flow cytometry for minimal residual disease detected the presence of blasts (expressing cCD3+, CD33+, and CD34+). To reduce the risk of infection, venetoclax (Day 1: 10 mg; Day 2: 20 mg; Day 3: 30 mg; Day 4-28: 100 mg), posaconazole, and decitabine (20 mg/m^2, mixed with normal saline, 150 mL for 5 d) were administered as chemotherapy-free induction therapy. Thereafter, no serious infection, such as febrile neutropenia, occurred. The patient underwent haploidentical peripheral blood cell transplantation after two additional cycles of venetoclax/decitabine.

OUTCOME AND FOLLOW-UP

The patient achieved CR one year post-HSCT. Figure 2 summarizes the absolute neutrophil counts from initiating the VPDL regimen to the end of the second venetoclax + decitabine cycle. Neutropenia resolved early during the second cycle. The ANC was less than 500 for two weeks and did not decline to less than 100.

DISCUSSION

Considering patients with MPAL, the three common treatment modalities include ALL-directed, AML-directed, and hybrid strategies (ALL plus AML). Based on retrospective data, experts favor ALL-based chemotherapy over AML-based chemotherapy owing to its superior remission rates [4,5]. However, accumulated data are retrospective, and validation in multicenter, prospective clinical trials is pending. Additionally, adverse effects associated with conventional treatment modalities, such as deadly infections and bleeding, present a persistent challenge to the survival of patients with MPAL[6]. A recent meta-analysis of 1300 patients found that patients who received an induction regimen with ALL-directed therapy were significantly more likely to achieve CR and were twice as likely to survive than patients who received an AML-directed regimen. The study included case reports of patients with MPAL (WHO) or biphenotypic leukemia (European Group for the Immunological Classification of Leukemias) as well as small international series and case reports. A multivariate examination of comprehensive clinical data, including the type of therapy, MPAL subgroup, and patient age, revealed that the overall survival (OS) rates between ALL and AML induction regimens did not differ (3-year OS, 48 6.9% versus 47 5.0%, respectively).

Hematopoietic stem cell transplantation has been shown to substantially increase the 5-year survival rate in patients with MPAL[7], and bridging therapy should ideally be associated with less toxicity and complications. Patients' survival was demonstrated to be considerably decreased by a combination regimen (a mix of ALL and AML therapy) (3-year OS, 23% 8.6%, P = 0.001), probably because of higher toxicity [4].

In November 2018, the Food and Drug Administration approved the administration of venetoclax along with an HMA in older or more vulnerable patients with recently diagnosed AML[8]. Venetoclax, a powerful oral BCL-2 inhibitor, has shown clinical success in treating various hematologic cancers[9]. In hematologic malignancies, HMAs act by inhibiting deoxyribonucleic acid (DNA) methyltransferase-1, which results in DNA demethylation, cell differentiation, or apoptosis[10]. The pathogenesis of myeloid and lymphoid malignancies is facilitated by aberrant DNA methylation, which has been

linked to the possibility that hematopoietic stem cells in MPAL undergo aberrant transformation[11]. According to recent real-world evidence, decitabine with venetoclax can yield superior outcomes to decitabine monotherapy in patients with AML[12].

Moreover, several clinical studies have indicated the potential feasibility of decitabine in B-cell ALL and T-cell ALL, especially R/R ALL, although data in this field remain limited[13–17]. Some case reports have indicated the efficacy of venetoclax in patients with MPAL[18]. The characteristics of T/myeloid MPAL are distinct from those of B/myeloid MPAL, another type of MPAL. A case of T/myeloid MPAL relapse following effective treatment of allo-HSCT with venetoclax + decitabine[19]. Given the challenges in conducting clinical trials targeting only the T/myeloid MPAL patient population, we present the third case report of a patient with T/myeloid MPAL successfully treated with venetoclax and an HMA.

CONCLUSION

Herein, we present a patient with MPAL who experienced serious complications with standard chemotherapy. Subsequently, the patient received combination therapy with venetoclax and HMA and underwent hematopoietic stem cell transplantation. Therefore, it is necessary to establish whether combination therapy with venetoclax and HMA could be beneficial as bridging therapy pre-transplantation. Accordingly, future investigations should compare the potential of venetoclax and HMA with traditional chemotherapy in patients who can eventually undergo transplantation.

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