Refractory Pediatric Acute Myeloid Leukemia expressing NUP98-NSD1 Fusion Gene Conquered by Venetoclax and DCAG

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Abstract

Pediatric AML with NUP98-NSD1 fusion defines a high-risk subset with a low remission and high relapse rates. There are a few studies on successful treatment of high-risk AML expressing NUP98-NSD1. We report a refractory pediatric case who received successful treatment with Bcl-2 inhibitor, venetoclax plus DCAG chemotherapy followed by HSCT, after two failure courses of conventional chemotherapies. Our case suggests that the combination of venetoclax and DCAG chemotherapy may be an effective salvage strategy to refractory AML with NUP98-NSD1. More studies and clinical trials should focus on the synergistic effect of Bcl-2 inhibitors and hypomethylation agents, especially in pediatric AML.

Introduction

Acute myeloid leukemia (AML) is a clonal hematopoietic stem cell malignancy, which is characterized by an accumulation of immature progenitor cells with arrested differentiation causing suppression of hematopoiesis [1]. Current treatment strategies for patients with AML include combination chemotherapy, hypomethylation agents (HMAs), and/or hematopoietic stem cell transplantation (HSCT), which are generally selected based on clinical, hematological and genetic prognostic indicators [2].

Nucleoporin 98 gene (NUP98) is fused to a variety of partner genes in a spectrum of hematologic malignancies, especially pediatric leukemias with poor prognosis [3]. Nuclear receptor-binding SET domain protein 1 (NSD1) is a member of histone methyltransferases family, which are essential in development and are mutated in AML, multiple myeloma, and lung cancers [4]. About 5% of human AMLs harbor the t (5;11) (q35; p15.5) translocation, which generates NUP98-NSD1 fusion gene [5]. Gang et al. identified that NUP98-NSD1 induced AML and sustained self-renewal of myeloid stem cells in vitro [4]. Later several largescale cohort studies of patients with AML have confirmed that the presence of NUP98-NSD fusion defines a high-risk leukemia subset with a low remission and high relapse rates [6, 7].

Despite our current knowledge of the molecular mechanisms and co-occurring genetic events of AML with NUP98-NSD1 fusion, the ability to effectively treat patients with these translocations is very limited. Current therapy strategies for AML patients with NUP98-NSD1 fusion often employ chemotherapy followed by hematopoietic stem cell transplantation (HSCT) during the first complete molecular remission. However, many patients could not achieve complete remission (CR) after conventional chemotherapy. For cases with poor remission status, salvage transplantation tends to have low success rates and high recurrence rates [8].

Here we present a case of successful treatment with decitabine, aclacinomycin, cytosine arabinoside (Ara-C), granulocyte-colony stimulating factor (DCAG) plus Bcl-2 inhibitor, venetoclax in a patient with AML (M2) expressing NUP98-NSD1 fusion, followed by allogeneic HSCT, who had never achieved CR after two courses of conventional chemotherapy regimens.

Case Description

A 3-year-old boy presented with fever for 4 days was admitted to our hospital. The blood count showed elevated white blood cells (WBC, 151G/L), decreased hemoglobin (Hb, 55g/L), neutrophil and lymphocyte percentage was 7.5% and 91.3%, respectively. The peripheral blood and bone marrow smear showed blasts were 79% and 73.5%, respectively. The flow cytometry of bone marrow identified 79.5% abnormal cell population of nuclear cells, which was positive for HLA-DR (91.94%), CD13 (76.22%), CD33 (94.25%), CD34 (30.43%), CD38 (79.99%), CD117 (96.76%), CD123 (98.93%), MPO (47.52%). The boy was diagnosed with AML (M2) and hyperleukemia, tentatively classified as intermediate risk.

Then the boy accepted the routine chemotherapy regimens according to China Childhood Leukemia Collaborative Group (CCLG)-AML 2019 guideline, which included Daunorubicin, Ara-C, Homoharringtonine (HHT) (DAH), followed by the second course of chemotherapy, IAH (Idarubicin, Ara-C, HHT). However, the boy could not achieve CR after two courses of chemotherapies. The results of the deep sequencing and RNA sequencing of hematological malignancies of this boy came out and found GATA2 mutation (NM_-032638:exon6:c.1154C¿T:p.P385L) and NUP98-NSD1 fusion gene. Consequently, the patient was classified as high-risk AML with NUP98-NSD1 fusion gene. The clinicians thought the routine chemotherapy could not help the patient, and more effective chemotherapy strategies must be employed. Thus, the clinicians collected the primary tumor cells of the patients to carry out a high-throughput drug sensitivity analysis (HDS) as a result of high-risk NUP98-NSD1 fusion.

Subsequently, the eight highly sensitive chemotherapy regimens were screened out according to the high-throughput drug sensitivity analysis of the patient's primary tumor cells (**Table 1**). However, the first four chemotherapy regimens contain the drugs that have been already employed in the two courses of conventional chemotherapy and have been proved ineffective. Besides, the NUP98-NSD1 fusion gene causes H3K36 methylation, resulting in leukemogenesis. Therefore, the clinicians finally chose the combination chemotherapy regimens of Bcl-2 inhibitor and DCAG, which includes hypomethylation agent decitabine ($20mg/m^2$), aclacinomycin ($10mg/m^2$), Ara-C ($10mg/m^2$), granulocyte-colony stimulating factor (125ug) and venetoclax tablets (DCAG plus venetoclax). Then the MRD gradually decreased to less than 10^{-4} on days 28 after DCAG plus venetoclax treatment. On the 35th day of this treatment, both of the MRD and bone marrow blasts became negative, and the NUP98-NSD1 fusion ratio decreased to 2.34%. The patient finally achieved CR after DCAG plus venetoclax therapy, then he underwent allo-HSCT with his HLA-haploidentical father as the donor. One month after transplantation, the blood count of the patient returned to normal, both of the peripheral blood and bone marrow blasts were negative, and flow cytometry showed MRD was less than 10^{-4}. Besides, IDH1 mutation, GATA2 mutation and NUP98-NSD1 fusion gene were both negative. The clinical course of this patient can be concluded in **Fig. 1** . This patient will have regular bone marrow examinations to be alert for recurrence.

Discussion

Targeting signaling pathways that regulate cell survival and death has emerged as an effective therapeutic strategy in patients with AML. Recently, numerous clinical trials have shown that the specific Bcl-2 inhibitor venetoclax combined with HMAs is effective in the treatment of relapsed and primary refractory AML. DiNardo et al. demonstrated that overall survival (OS) was longer and the incidence of remission was higher among patients who received azacitidine plus venetoclax than among those who received azacitidine alone in a randomized clinical trial (NCT02993523) [9]. In a phase 3 clinical trial, Wei et al. identified that venetoclax plus low-dose cytarabine (LDAC) improved remission rate and OS compared to LDAC alone (NCT03069352) [10]. Then Karol et al. demonstrated the safety and activity of venetoclax plus chemotherapy in pediatric patients and indicated that this combination could be employed in newly diagnosed pediatric patients with high-risk AML [11]. Overall, venetoclax in combination with HMAs improves the prognosis of older patients with AML, but there are a few clinical trials about pediatric AML.

Our patient was diagnosed with NUP98-NSD1 fusion gene, IDH1 mutation, and GATA2 mutation by RNA sequencing, which make him to be classified to high-risk group. Isocitrate dehydrogenase 1 and 2 (IDH1

and IDH2) gene mutations were reported in 19% of newly diagnosed AML patients [12]. Though the drugs targeting IDH1 mutation ivosidenib have been approved, it is too expensive and unacquirable for the patient. Besides, the IDH1 mutation frequency became very low after two courses of conventional chemotherapy. However, the MRD was still very high (50%), which was mainly caused by the high expression level of NUP98-NSD1 fusion gene (75.94%). Kivioja et al. screened patient cells and engineered cell models with over 300 compounds, and found that the cells expressing NUP98-NSD1 had significantly increased sensitivity to Bcl-2 inhibitors [13]. However, there are no reports on venetoclax plus decitabine use in pediatric patients with AML expressing NUP98-NSD1 fusion.

Here we firstly employed DCAG plus venetoclax to treat the patient with NUP98-NSD1 fusion who could not achieve CR after two courses of chemotherapy. The combination therapy of Bcl-2 inhibitor venetoclax and HMAs (decitabine) had a promising outcome, and the patient achieved CR which made him to be able to accept HSCT. Overall, venetoclax could be effective and safe for treating pediatric AML expressing NUP98-NSD1 fusion. Therefore, establishing the appropriate dosage, efficacy, and safety of venetoclax in pediatric patients through clinical trial is required. Further genetic and pharmacological studies of AML with NUP98-NSD1 fusion are urgently needed to improve patient outcomes.

Ethics Statement

The patients provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

HX and HY collected the data and drafted the manuscript, and are the co-first authors. JX, XW, FZ, ST, XF, QL, BZ helped collect the data and discussed the case. RJ and HC reviewed and finalized the manuscript. All authors had the approval of the version to be published.

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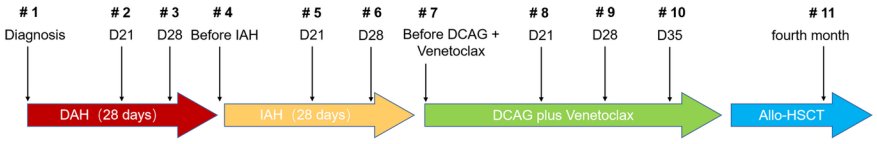
Figure Legends

Figure 1. Clinical course of the patient. DAH, daunorubicin (40 mg/m^2), cytosine arabinoside (100mg/m^2), homoharringtonine (3 mg/m^2); IAH, idarubicin (10 mg/m^2), cytosine arabinoside (100mg/m^2), homoharringtonine (3 mg/m^2); DCAG, decitabine (20 mg/m^2), aclacinomycin (10 mg/m^2), cytosine arabinoside (10 mg/m^2), granulocyte-colony stimulating factor (125μg).



Time Point	# 1	# 2	# 3	# 4	# 5	# 6	# 7	# 8	# 9	# 10	# 11
Peripheral blood blasts %	**79**	0	0	55	20	2	25	0	0	0	**0**
Bone marrow blasts %	**73.5**	29	13.5	69	59.5	54.5	48.5	19	4	0	**0**
MRD %	**79.5**	36	22.5	62	86	50	49	4.5	$< 10^{-4}$	$< 10^{-4}$	**$< 10^{-4}$**
IDH1 %	**22.5**		11.9			0.88		0.14		0	**0**
GATA2 %	**1.1**		0								**0**
NUP98-NSD1 %	+		+			75.94		17.69	3.35	2.34	**0**

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`TABLE 1.docx` available at https://authorea.com/users/323903/articles/571884-refractory-pediatric-acute-myeloid-leukemia-expressing-nup98-nsd1-fusion-gene-conquered-by-venetoclax-and-dcag