Clinical and Biological Characteristics of 14 Adult Cases of *NUP98-NSD1*$^+$ Acute Myeloid Leukemia

NUP98-NSD1$^+$ Akut Myeloid Lösemi Tanılı 14 Erişkin Hastada Klinik ve Biyolojik Özellikler

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To the Editor,

The 11p15 chromosome rearrangement could lead to the rearrangement of the nucleoporin 98 gene (*NUP98*), forming a new fusion gene [1]. The *NUP98-NSD1* fusion gene occurs as a result of a cryptic t(5;11)(q35.2;p15.4) chromosomal translocation, in which the 12th exon of the N-terminal of the *NUP98* gene is connected to the 6th exon of the C-terminal of the *NSD1* gene, forming a chimeric protein [2]. The incidence of *NUP98-NSD1* in pediatric acute myeloid leukemia (AML) is 3.8% [3]. Patients with *NUP98-NSD1* in AML usually have a normal karyotype [4]. Among pediatric and adult AML patients with normal chromosomal karyotypes, the positivity rates are 16.1% and 2.3% [5]. Extensive research on pediatric *NUP98-NSD1*$^+$ AML patients has been conducted, but there are few studies on *NUP98-NSD1*$^+$ adult AML patients.

A total of 507 adult patients with newly diagnosed AML were admitted to the Department of Hematology of the First Affiliated Hospital of Soochow University between January 2014 and March 2019 and included in this study. Chromosomal karyotype analysis was performed using a direct method with bone marrow cells and/or a short-term culture method. Sequencing was performed using second-generation DNA sequencing technology [6]. Continuous data with non-normal distribution were represented by M (Q1, Q3) values, and discrete data were represented by cases.

Among the 507 patients, 14 individuals (2.76%) tested positive for the *NUP98-NSD1* gene, including 7 men and 7 women with a median age of 33.5 (18-51) years. The median white blood cell count was 43.8x10^9/L (5.5-193.6x10^9/L) and the median bone marrow blast percentage was 72.05% (43%-90.5%). According to the FAB classification, the majority of cases were M1 (4/14), M4 (3/14), or M5 (5/14). Half of the cases (7/14, 50%) were associated with a normal karyotype. Based on the 2017 European LeukemiaNet risk stratification, 4 patients were in the high-risk group, 5 the medium-risk group, and 5 the low-risk group. Among these 14 patients, 4 patients (28.57%) also had the *FLT3-ITD* mutation, 3 patients (21.43%) had a biallelic mutation of *CEBPA*, and 2 patients (14.29%) had the *KMT2C*, *WT1*, and *DNMT3A* mutations, respectively (Table 1).

All 14 patients received IA or DA+AAG regimens for induction chemotherapy, followed by conventional consolidation regimens of chemotherapy. One patient consistently had no response (NR) to multiple courses of chemotherapy, 2 patients had partial response (PR), and 2 patients relapsed after remission (Table 1). The results showed that adult *NUP98-NSD1*$^+$ AML is a very invasive disease with a poor prognosis. It was difficult to achieve remission through chemotherapy and the patients were prone to disease recurrence and progression. All 14 patients subsequently underwent hematopoietic stem cell transplantation, with 9 patients dying within 1-15 months after transplantation (4 dying from graft-versus-host disease, 3 from relapse, and 2 from infection) and 5 patients surviving. The median overall survival was 14 months. Among the 4 *FLT3-ITD*$^+$/*NUP98-NSD1*$^+$ patients, 3 died (75% mortality) and 1 survived. Both *DNMT3A*$^+$/*NUP98-NSD1*$^+$ patients died (100% mortality).

In conclusion, adult *NUP98-NSD1*$^+$ AML patients usually have a younger onset age and higher tumor burdens. These patients have poor prognosis, especially those with concomitant *FLT3-ITD* or *DNMT3A* mutations. Screening for the *NUP98-NSD1* gene should be routinely performed for the initial diagnosis of AML patients to identify this high-risk anomaly early in order to evaluate prognosis.

Keywords: Acute myeloid leukemia, Adult, *NUP98-NSD1*, Characteristics

Anahtar Sözcükler: Akut myeloid lösemi, Erişkin, *NUP98-NSD1*, Özellikler

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Table 1. Basic information and clinical characteristics of adult patients with *NUP98-NSD1*⁺ acute myeloid leukemia.

No.	Sex	Age	WBC ($x10^9$/L)	BM blasts (%)	FAB type	Karyotype	Mutations	Induction chemotherapy regimen	Chemotherapy effect	HSCT subtype	Prognosis
1	F	19	62.14	80.0	M5	+6	*FLT3-ITD* *SETBP1*	IA	Relapse	Unrelated	Death
2	M	18	159	48.0	M4	+8	*CAF1R* *WT1* *NOTCH1*	IA	PR	Haplo	Death
3	F	50	11.9	67.5	M5	11p15 abnormal	*FLT3-ITD* *NRAS* *RUNX1*	DAC+AAG	NR	Sibling	Death
4	F	39	49.78	58.0	M2	Normal	*FLT3-ITD* *KRAS*	IA	Relapse	Haplo	Death
5	F	37	9.0	43	M4	inv(16)	*FLT3-TKD* *KIT*	IA	CR1	Unrelated	Survival
6	M	24	16.92	74.5	M1	Complex	*ETV1* *KMT2C*	IA	CR1	Haplo	Death
7	M	22	5.5	88.5	M1	Normal	*biCEBPA* *EZH2* *FLT3-ITD* *WT1* *IKZF1*	IA	CR1	Haplo	Survival
8	F	46	105	90.5	M5	11p15 abnormal	*DNMT3A*	IA	PR	Unrelated	Death
9	F	40	101	80.5	M5	Normal	-	IA	CR1	Sibling	Survival
10	M	30	14.8	47.0	M4	Normal	*KRAS*	IA	CR1	Unrelated	Survival
11	F	51	43.8	65.5	M5	11p15 abnormal	*DNMT3A*	DAC+AAG	CR1	Unrelated	Death
12	M	33	24.86	84.6	M1	Normal	*biCEBPA* *KMT2C*	IA	CR1	Haplo	Survival
13	M	18	123	69.6	M2	Normal	*biCEBPA* *CSF3R*	IA	CR1	UCBT	Death
14	M	34	193.6	85.5	M1	Normal	*NPM1*	IA	CR1	Sibling	Death

WBC: White blood cell count, BM: bone marrow, NR: no response, PR: partial response, CR1: first complete remission, Haplo: haploidentical stem cell transplantation, Sibling: sibling stem cell transplantation, UCBT: umbilical cord blood transplantation.

Ethics

Informed Consent: Written informed consent was obtained from all patients and their families.

Authorship Contributions

Surgical and Medical Practices: Y-J.S., S-Q.L.; Concept: Y-J.S., L-R.L.; Design: Y-J.S., L-R.L.; Data Collection or Processing: W.W., S-Q.L.; Analysis or Interpretation: Y-J.S., W.W., S-Q.L., L-R.L.; Literature Search: Y-J.S., W.W.; Writing: Y-J.S., W.W., S-Q.L., L-R.L.

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