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CLINICAL CHARACTERISTICS AND OUTCOMES OF NUP98 REARRANGEMENT IN ADULTS WITH ACUTE LEUKEMIA

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INTRODUCTION

- Genetic rearrangements involving *NUP98* located on chromosome 11p15.4 are commonly associated with therapy resistance in pediatric leukemia. However, the outcomes of *NUP98* rearrangements (*NUP98r*) in adult leukemias are largely unknown.
- Acute leukemia with *NUP98r* is characterized by upregulation of the *HOX* genes and a dependency on the menin-KMT2A interaction where menin inhibition led to an antileukemic activity in preclinical *NUP98r* models.[1]
- Given the advent of menin inhibitors as a successful therapeutic strategy in these genetically defined leukemia subsets, a better recognition of this entity in adults is needed.

AIM

The aim of this study is to describe the clinical characteristics and outcomes of patients with a *NUP98* rearranged leukemia.

METHODS

Patients seen at MD Anderson were screened for *NUP98r* either by conventional cytogenetics, fluorescence in situ hybridization (FISH) or optical genome mapping (OGM). For this analysis, only those patients with confirmed *NUP98r* by FISH or OGM were included.

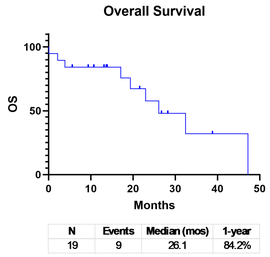
RESULTS

- Nineteen patient were identified to have a *NUP98r*
- Baseline characteristics are shown below:

Patients, n (%)	19 (100)
Median age, y (range)	42 (3-85)
Male, n (%)	9 (47)
WBC, median x 10^9/L (range)	5 (0.2-334)
Platelet count, median x 10^9/L (range)	70 (23-290)
Peripheral blast %, median (range)	30 (1-90)
BM Blast %, median (range)	66 (12-97)
AML, n (%)	16 (84)
T-ALL, n (%)	2 (11)
CML-BC, n (%)	1 (5)
Cytogenetics	
Normal, n (%)	6 (32)
t(11p15), n (%)	8 (42)
Other, n (%)	5 (26)
Co-Mutations	
WT1, n (%)	10 (53)
FLT3-ITD, n (%)	8 (42)
FLT3 (other), n (%)	4 (21)
PTPN11, n (%)	4 (21)
KRAS/NRAS, n (%)	3 (16)
RUNX1, n (%)	3 (16)
TET2, n (%)	3 (16)
IDH1, n (%)	1 (5)
IDH2, n (%)	1 (5)
TP53, n (%)	1 (5)
Lines of therapy	
0, n (%)	1 (5)
1, n (%)	5 (26)
2, n (%)	4 (21)
≥3, n (%)	9 (47)

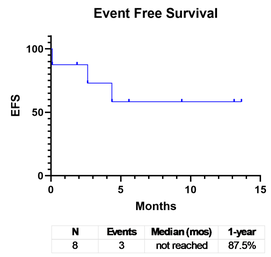
Table 1. Baseline Characteristics. BM, bone marrow; WBC, white blood cell.

- Translocations seen in these patients include:
  - t(5;11)(q35:p15) - *NSD1:NUP98*
  - t(11;20)(p15;q11.2) - *TOP1:NUP98*
  - Translocation involving *NUP98, YY1, BCL11B*
  - t(11;15)(p15;q15)
  - t(7;11)(p14;p15)
  - t(11;12)(p15;q12)
  - t(4;11)(q31.1;p15)
- The most common co-mutations included *WT1*, *FLT3-ITD*, and *PTPN11* (Table 1).
- Following frontline therapy, 12 patients achieved a complete remission (63%).
- With a median follow-up of 26.7 months, the median overall survival (OS) for patients with *NUP98r* was 26.1 months with a 2-year OS rate of 57.7%. (Figure 1)
- There was no difference in outcomes by *FLT3* mutational status. (Figure 3)
- In a landmark analysis set at 5 months, patients who underwent stem cell transplantation in consolidation (n=13) had an improved overall survival compared to those who did not (median of 32.5 vs 17.1 months; p-0.0027). (Figure 4)



N	Events	Median (mos)	1-year
19	9	26.1	84.2%

Figure 1. Overall survival for all patients with *NUP98r*



N	Events	Median (mos)	1-year
8	3	not reached	87.5%

Figure 2. Event free survival for those seen initially at MD Anderson

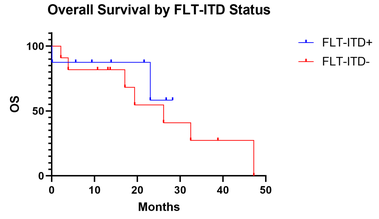


Figure 3. Overall survival by *FLT-ITD* mutational status

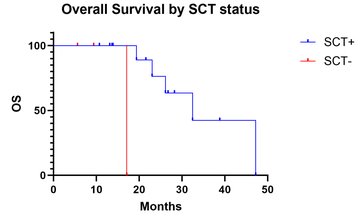


Figure 4. Overall survival by those receiving stem cell transplantation (SCT) vs those who did not

CONCLUSIONS

- Acute leukemia with *NUP98r* is a rare entity particularly in adults.
- *NUP98r* can often be missed by conventional cytogenetics and methods such as FISH and OGM may identify some of these patients.
- *NUP98r* frequently co-occur with other mutations such as those in *WT1*, *FLT3*, and *PTPN11.*
- More work will be needed to further investigate therapies and improve outcomes for leukemias harboring these rearrangements.

REFERENCES

1. Heikamp EB, Henrich JA, Perner F, et al. The menin-MLL1 interaction is a molecular dependency in NUP98-rearranged AML. *Blood*. 2022;139(6):894-906. doi:10.1182/blood.2021012806

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