Clinicopathological Features, Co-mutational Patterns and Outcomes in *NPM1*-mutated Adult Acute Myeloid Leukemia Patients Treated at Singapore General Hospital

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INTRODUCTION

Nucleophosmin *(NPM1)* mutations occur in approximately 30% of adult cases of acute myeloid leukemia (AML) and are typically associated with a more favorable prognosis. However, recent evidence suggests that the type of *NPM1* mutations and co-mutations may influence outcomes (1).

This analysis assessed the real-world clinico-pathological features, co-mutations and outcomes in *NPM1*-mutated AML patients diagnosed at Singapore General Hospital.

METHOD

AML patients aged 18 years and above with *NPM1* mutations identified via Sanger or next-generation sequencing (NGS) from 2017 to 2025 were studied. The Oncomine Myeloid Research assay (Themo Fisher Scientific, USA) was used to interrogate 40 DNA genes. NGS libraries were sequenced with Ion GeneStudio S5 System (Thermo Fisher Scientific) and analysed using in-house bioinformatics pipelines and the IonReporter™ software. Measurable residual disease (MRD) was detected using quantitative polymerase chain reaction (qPCR). Clinical data was collected from medical records. The study was approved by the institutional review board.

RESULTS

71 patients were identified, of which 59 underwent treatment and follow up (see table 1 for patient cohort characteristics). 61 patients (85.9%) had a normal karyotype, with none being complex. Co-mutational patterns are illustrated in figure 1. *FLT3*-internal tandem duplications (ITD) (53.5%), *DNMT3A (46.5%)* and *TET2 (26.8%)* mutations were the most common. Myelodysplasia-related gene mutations were not frequently encountered (11.3%).

59 patients received treatment, of which 39 (66.1%) received intensive chemotherapy with a median follow up of 23.2 months. 89.7% achieved a complete response, with 41% becoming *NPM1*-MRD-negative after 2 cycles of chemotherapy. Median overall survival (OS) was not reached, and 5-year OS was 66% (figure 2A). 23 patients (39%) underwent allogeneic hematopoietic stem cell transplantation. Post-transplant, 2 patients had molecular relapse but 1 progressed to full hematologic relapse. In contrast, 33.9% of patients received non-intensive treatment with a median follow up of 25.8 months and median OS of 19.8 months (p=0.0002, figure 2A).

Despite recent data (2) suggesting that patients with co-existent *FLT3*-ITD and *DNMT3A* mutations have less favourable outcomes, this pattern was not identified in our cohort. There was also no significant difference in OS between type A and non-type A *NPM1* mutations (figure 2B), consistent with previous published data (3).

CONTACT INFORMATION

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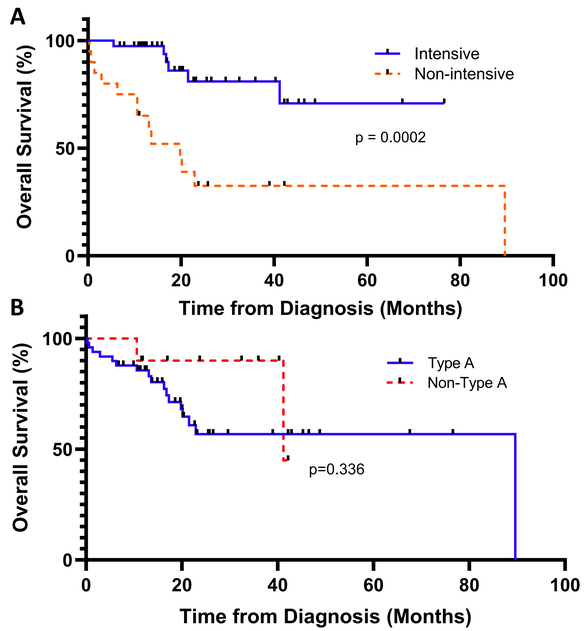

Figure 2: Overall survival in patients undergoing intensive and non-intensive treatments (A); overall survival in patients with *NPM1* type A and non-type A mutations (B)

CONCLUSIONS

NPM1-mutated AML typically has a normal karyotype with commonly co-mutated *FLT3-ITD (53.5%)*, *DNMT3A (46.5%)* and *TET2 (26.8%)*. Myelodysplasia-related gene mutations were less common (11.3%). Overall survival in those receiving intensive treatment was significantly better than in those receiving less intensive treatment. *NPM1* mutation subtype was not shown to affect survival outcomes, consistent with previous data (2).

REFERENCES

(1) Othman *et al.* Blood (2024); 144(7):714-728
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Total number of patients	71
Median age at diagnosis, years (IQR)	62 (54-71)
Male, n (%)	34 (47.9)
Race, n (%)	
Chinese	51 (71.8)
Malay	14 (19.7)
Indian	3 (4.2)
Others	3 (4.2)
ELN 2022 Risk Classification, n (%)	
Favourable	31 (43.7)
Intermediate	36 (50.7)
Adverse	4 (5.6)
ELN 2024 Risk Classification, n (%)	
Favourable	21 (29.6)
Intermediate	50 (70.4)
Adverse	0
Extramedullary disease, n (%)	3 (4.2)
WBC at presentation (x10^9/L), median (IQR)	47.3 (21.4-136)
Karyotype, n (%)	
Normal	61 (85.9)
Adverse Risk (by ELN 2022)	0
Complex	0
Unknown	2 (2.8)
***NPM1* Mutation Subtype, n (%)**	
A	58 (81.7)
B	4 (5.6)
D	5 (7)
I	3 (4.2)
Unknown	1 (1.4)
Number of treated patients	59
Median follow up, months	23.7
Median overall survival, months	89.6
Type of induction treatment, n (%)	
3 + 7	24 (40.7)
3 + 7 + midostaurin	15 (25.4)
Azacitidine and venetoclax	13 (22)
Others (low intensity)	7 (11.9)
Response post induction (all patients), n (%)	
CR	47 (79.7)
CRi	1 (1.7)
PR	1 (1.7)
Refractory	6 (10.2)
Reponse post intensive induction, n (%)	
CR	35 (89.7)
PR	0
Refractory	4 (10.3)
Received alloHSCT, n (%)	23 (39)

Table 1: Patient cohort characteristics; number of patients (n), interquartile range (IQR), European LeukaemiaNet (ELN), total white cell count (WBC), idarubicin or daunorubicin with cytarabine (3+7), response criteria as per ELN 2022 guidelines – complete response (CR), complete response with incomplete haematologic recovery (CRi), partial response (PR), allogeneic haematopoietic stem cell transplant (alloHSCT)

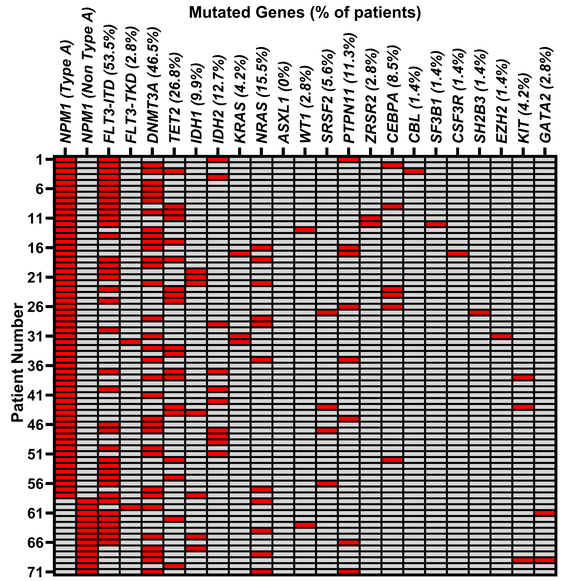

Figure 1: Heatmap illustrating co-mutations in each patient – each patient is represented by a row; red (mutation detected by NGS), grey (no mutation detected by NGS)