Redefining prognostication of *de novo* cytogenetically normal acute myeloid leukaemia in young adults

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Abstract

Cytogenetically normal acute myeloid leukaemia (CN-AML) showed diverse mutations and clinical outcomes. Next generation sequencing (NGS) was performed at diagnosis. *DNMT3A* mutation improved prognostication when incorporated as an adverse risk factor. Prediction model based on clinical and genetic data by machine learning performed better than the European LeukemiaNet (ELN) ELN based model.

Introduction

CN-AML is the largest cytogenetic subgroup of AML, occurring in 50% of cases. It is heterogeneous with diverse mutations and prognoses. The ELN guideline categorized AML into favourable, intermediate and adverse risk groups based on cytogenetic and mutation features but its application in CN-AML has not been formally tested.

Methodology

- Young patients (≤ 60 years old) with *de novo* CN-AML diagnosed between 2003-2019 were recruited.
- Treatment regimen: "7+3" induction followed by up to 4 courses of high dose cytarabine consolidation. Allogeneic haematopoietic stem cell transplantation (HSCT) decision was based on ELN guidance and clinical grounds.
- Mutations / clonal architectures were identified by NGS.
- The clinical and genetic data formed a databank from which prediction model was built by machine learning.

Figure 1. Mutation spectrum of 401 patients.

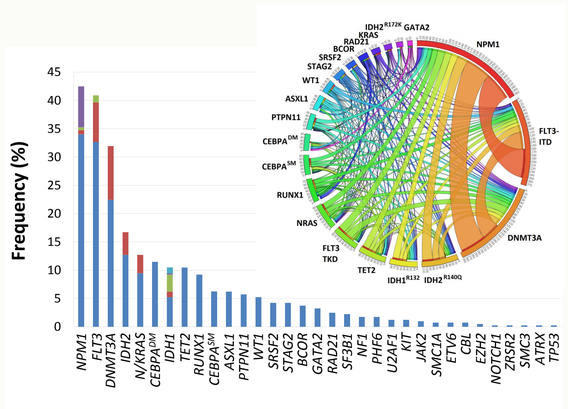

Figure 2. Clonal heterogeneity in CN-AML.

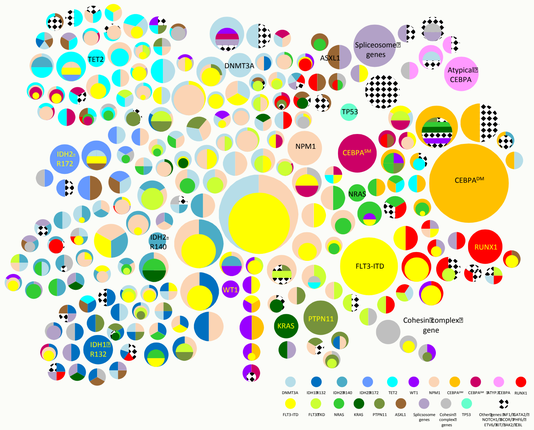

Figure 3. (A) LFS and (B) OS after incorporating *DNMT3A* mutation as unfavorable risk group.

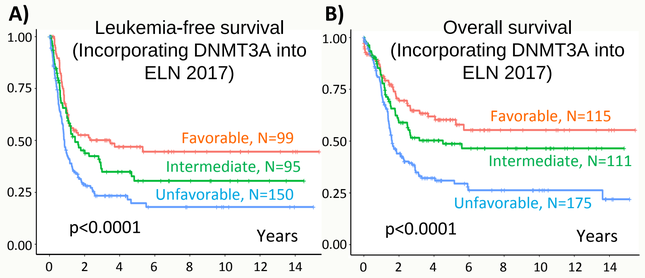

Figure 4. (A) Sediment plots of two hypothetical patients who received allo-HSCT at CR1 or not. (B) Concordance index of study cohort (training set) and CN-AML patients (≤ 60 year-old) in TCGA cohort (validation set).

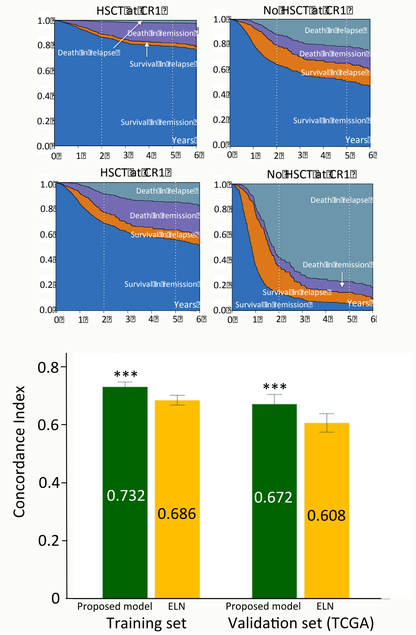

Table 1. Clinicopathologic characteristics of *de novo* CN-AML patients

Features	Number	Percentage
Gender M/F	199/260	
Age (Median, Range) (Years)	49 (18-60)	
Presenting WCC (Median, Range) (x10^9/L)	21.6 (0.25-445.6)	
Bone marrow blast % (Median, Range)*	69.4 (15-99)	
Achieved CR/CRi	396	86.27
After 1 course of induction	283	71.46
After 2 courses of induction	81	20.45
≥ 3 courses of induction	32	8.08
Received HSCT †	182	39.65
At CR1	108	59.34
At CR2	63	34.62
At CR3	3	1.65
At relapsed state	8	4.40

* One patient with BM blasts 15% showed 32% blasts in PB
† One patient received autologous HSCT

Results and Discussion

459 patients were recruited and their clinicopathologic features were shown in Table 1. 401 patients with diagnostic NGS performed. *NPM1, FLT3* and *DNMT3A* mutations were the most common, occurring in 30-40% cases (Figure 1). Clonal architectures were extremely heterogeneous as shown in Figure 2, where the size of the bubble represented the frequencies of occurrence and the outer and inner bubbles indicated dominant and sub-clones. Individual mutations were colour coded. Prognostic impacts of DNMT3A mutation overrode those of *NPM1* and *FLT3* mutations and when incorporated as adverse risk factor, it improved prognostication by ELN (Figure 3). Machine learning resulted in a predication model (https://redefiningprognosis.shinyapps.io/denovo_cnaml/) that might inform clinical decision with respect to allo-HSCT at CR1. Based on concordance index, its performance compared favorably with that of ELN prediction, both in our cohort and in TCGA (The Cancer Genome Atlas) validation cohort (Figure 4).

Conclusion

NGS and machine learning are powerful tools that have shed light to the mutation landscape of AML and improved our ability to predict outcome and inform clinical decision. The prediction model described herein might provide personalized guidance for AML patients.

Acknowledgements

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