

Characterizing the Molecular Abnormalities in Rare *De Novo* Ph⁺ Acute Myeloid Leukemia

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To the Editor: The t(9;22)(q34;q11) (Philadelphia chromosome [Ph]) balanced translocation results in fusion of the *BCR* gene at 22q11 with cytoplasmic tyrosine kinase gene *ABL1* and plays an essential role in leukemic transformation. The Ph is an infrequent finding in *de novo* acute myeloid leukemia (AML), approximately 0.5–3% of newly diagnosed patients.^[1] The World Health Organization (WHO) recently released a revised version of the Classification of Hematopoietic and Lymphoid Malignancies, a new provisional category of AML with *BCR-ABL1* was added to recognize these rare Ph⁺ AML cases that could benefit from tyrosine-kinase inhibitor (TKI) therapy.^[2] It is required to enlarge the sample size and research the molecular or genomic features to increase the argument in favor of Ph⁺ AML as a real entity.

A total of 5402 Chinese patients with *de novo* AML were identified from the database of the Department of Hematopathology at Medical University of Suzhou and Affiliated Changzhou Second Hospital of Nanjing Medical University for the period from September 2005 to October 2016. Ph⁺ AML was defined as cases fulfilling the current WHO criteria for AML that bore the t(9;22)(q34;q11) or variant (9;22) translocation on bone marrow cytogenetics, had no history of chronic or accelerated phase chronic myeloid leukemia (CML) before diagnosis, no evidence of a CML-like picture following therapy for AML, no presence of splenomegaly or basophilia (defined as >2% of basophils in peripheral blood) suggestive of a myeloproliferative neoplasm, and no history of chemotherapy and/or radiation therapy.^[1-3] Cases fulfilling diagnostic criteria of the 2016 WHO classification for acute ambiguous lineage leukemia were also excluded from the study.^[2]

The overall incidence of *de novo* Ph⁺ AML among all cases of AML was 0.22% (12/5402). The frequency (0.22%) is lower than the previous study; we believe that the stringent exclusion criteria used may explain the lower frequency.

Next-generation sequencing (NGS) was available in seven patients using a custom-designed 49 genes⁺ panel (Ion S5™ System, Thermo Fisher, San Diego, CA, USA), including the entire coding region

of *ASXL1*, *ASXL2*, *BCOR*, *BCORL1*, *BIRC3*, *BRAF*, *CALR*, *CBL*, *CDKN2A*, *CSF3R*, *CSMD1*, *DNMT3A*, *ETNK1*, *ETV6*, *EZH2*, *FBXW7*, *FLT3*, *GATA2*, *IDH1*, *IDH2*, *IL7R*, *JAK1*, *JAK2*, *JAK3*, *KIT*, *KRAS*, *MPL*, *MYD88*, *NOTCH1*, *NRAS*, *PAX5*, *PDGFRA*, *PDGFRB*, *PHF6*, *PIGA*, *PTEN*, *PTPN11*, *RUNX1*, *SETBP1*, *SETD2*, *SF3B1*, *SH2B3*, *SRSF2*, *STAG2*, *TET2*, *TP53*, *U2AF1*, *WT1*, and *ZRSR2*, with a median depth of ×2000. *FLT3*-ITD, *NPML*, and *CEBPA* mutations were detected by DNA-based polymerase chain reaction.

Overall, six patients harbored at least one mutation. The frequently mutated genes, in order of mutation prevalence, were *RUNX1* (3/7), *IDH1* (2/7), *ASXL1* (1/7), *ASXL2* (1/7), *NRAS* (1/7), *KRAS* (1/7), *TET2* (1/7), *DNMT3A* (1/7), and *CSMD1* (1/7). Detailed data are summarized in Table 1.

Clinical data were available in 12 patients with follow-up extending from 45 days to 11 years after diagnosis, and the median survival time was 17.5 months. Among three *RUNX1*-mutated patients, two patients achieved complete remission (CR) and one patient did not have any response to traditional chemotherapy. We found no difference in CR rate between patients with *RUNX1*^{mut} and *RUNX1*^{wild} type (2/3 vs. 3/4, *P* = 0.809). Six of the seven patients received allogeneic hematopoietic stem cell transplantation (allo-SCT) in first CR and one patient (Case No. 8) received allo-SCT in partial remission condition. Among these seven patients, six patients, except the case No. 12, received TKI at diagnosis. All patients with *RUNX1* mutations eventually relapsed and were trended toward reduced overall survival (OS, median: 19 vs. 62 months) as compared to patients with *RUNX1* wild type. Interestingly, the patient (Case No. 12) who had

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Table 1: Clinical and laboratory features of 12 cases with Philadelphia chromosome-positive AML

Case number/ gender/age (years)	WBC ($\times 10^9/L$)	Therapy regimens	NGS	Outcomes
1/male/19	307.7	Chemotherapy, TKI, and HSCT	<i>RUNX1</i> (Y406fs)	CR, relapsed in 10 months after diagnosis and died 1 month later
2/male/30	31.17	Chemotherapy, TKI, and HSCT	<i>NRAS</i> (Q61K), <i>KRAS</i> (G12V) <i>CSMD1</i> (R2897S)	Failed to achieve CR, died of GVHD, the OS time is 3 months
3/male/42	92.92	Chemotherapy, TKI, and HSCT	<i>DNMT3A</i> (G10R), <i>ASXL2</i> (R584)	CR, stable and alive for over 5 years
4/male/37	45.87	Chemotherapy, TKI, and HSCT	No mutation was found	CR, stable and alive for 13 months
5/male/47	59.3	Chemotherapy and TKI	NA	CR, stable and alive for 21 months
6/male/29	24.9	Chemotherapy, TKI, and HSCT	<i>RUNX1</i> (H105Q), <i>ASXL1</i> (G1339) <i>IDH1</i> (R132C), <i>TET2</i> (R1572W)	CR, relapsed in 16 months after diagnosis and died 2 months later
7/male/18	151.2	Chemotherapy and TKI	NA	Failed to achieve CR, the OS time is 4 months
8/female/28	69.0	Chemotherapy, TKI, and HSCT	<i>RUNX1</i> (R166Q)	Failed to achieve CR, relapsed in 16 months after HSCT and died 45 days later
9/female/45	15.4	Chemotherapy and TKI	NA	Failed to achieve CR, died in 11 months
10/female/31	99.28	Chemotherapy and TKI	NA	CR, died of relapse in 18 months
11/male/45	17.8	Chemotherapy	NA	Died of severe infections during induction chemotherapy
12/male/40	17.2	Chemotherapy and HSCT	<i>IDH1</i> (R132C)	CR, stable and alive for over 10 years

AML: Acute myeloid leukemia; WBC: White blood cell count; NGS: Next-generation sequencing; TKI: Tyrosine-kinase inhibitor; HSCT: Hematopoietic stem cell transplantation; CR: Complete remission (after induction chemotherapy); GVHD: Graft-versus-host disease; OS: Overall survival; NA: Not available.

IDH1R132 as a solitary abnormality achieved rapidly remission after chemotherapy; subsequently, the allo-SCT was treated and the disease-free survival time had been beyond 10 years; notably, the TKI therapy was not employed.

Numerous data confirmed that *RUNX1* mutation was a significant predictor for resistance to standard chemotherapy and for inferior survival. A portion (3/7) of this Ph⁺ AML cohort was found to carry *RUNX1* mutations, strong higher than previously published data in other series.^[4] *RUNX1* mutations have been described not to be able *per se* to cause full-blown leukemia;^[5] the coexistence of *BCR-ABL1* and *RUNX1* mutations in this study raises the possibility of synergistic effect between two genetic alterations on leukemogenesis. Similar to what has been reported in adult AML patients, our observations suggest that *RUNX1* mutations may also be associated with poor outcome in Ph⁺ AML, which could be explained by an association with reduced OS. However, we could not draw a definitive conclusion because of the small number of Ph⁺ AML patients.

The frequency of *IDH* mutations is clearly low in CML, and there were no reports in Ph⁺ AML patients except these our cases. Our data demonstrated that the patient who had *IDH1R132* as a solitary molecular abnormality remained in CR at the most recent follow-up in October 2016 (beyond 10 years after allo-SCT), he received no TKI. Recent data showed that Ph⁺ AML patients could benefit from the added therapy with TKI; however, it was important to note that massive mutational screening by NGS had not been performed, a novel concept based on NGS is critically needed.

In summary, our identification of only 12 Ph⁺ AML cases in an 11-year period at two large institutions confirms that this is an extremely rare disease. Ph⁺ AML cases carried *RUNX1* mutations

at a higher frequency to that in AML patients in general, and all these patients died of relapse even undergoing allo-SCT. On the contrary, seemingly Ph⁺ AML patient with mutation in *IDH1R132* could be remissioned by allo-SCT, even without TKI. Further bigger studies utilizing NGS methods may provide guidance for Ph⁺ AML prognostic stratification and clinical management.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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