



The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

612.ACUTE LYMPHOBLASTIC LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

Dynamic Changes in ABL1 Kinase Domain Mutations and Comparative Efficacy of Third-Generation Tyrosine Kinase Inhibitors across Different Stages in Acute Lymphoblastic Leukemia and Chronic Myeloid Leukemia Blast Crisis Patients

Zixuan Li, MS¹, Danyue Peng, PhD¹, Jun Deng, MD PhD², Lv Xiong, MSc¹, Ping Yin, PhD³, Jing Hu, PhD³, Chenjing Qian, MD¹, Lan Yao, PhD¹, Hua Yin, MD⁴, Mei Hong, MD¹, Qiuling Wu, PhD⁵

¹ Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

² Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

³ Department of Epidemiology and Biostatistics, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

⁴ Institute of Hematology, The Fifth Medical Center of PLA General Hospital, Beijing, China

⁵ Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

*Drs.Zixuan Li and Danyue Peng contributed equally. Drs.Mei Hong and Qiuling Wu are co-corresponding authors

Background

The development of first-generation and second-generation tyrosine kinase inhibitors (TKIs) has played a crucial role in the treatment of Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL) and chronic myeloid leukemia (CML). However, the emergence of mutations in the kinase domain (KD) of *BCR-ABL1* has increasingly compromised the efficacy of TKIs and become the primary cause of TKI resistance. Testing *BCR-ABL1* KD mutations in early phase accurately is of great value in predicting response and guiding therapeutic decisions. Next-generation sequencing (NGS) provided a more comprehensive and elaborate understanding of mutation status. Third-generation (3G) TKI has been designed to overcome resistance problems caused by *BCR-ABL1* KD mutations, and it exhibited unique pharmacological profiles and response patterns relative to different mutations and disease characteristics. Therefore, the potential clinical relevance of mutations detected by NGS and the efficacy of 3G TKI are worth exploring.

Methods

NGS was used to analyze the dynamic changes of both clinically unreported mutations and reported resistant mutations in the *ABL1* KD during three stages of the disease course (pretreatment, remission, and relapsed periods) in Ph+ ALL (n = 97) and chronic myeloid leukemia blast crisis (CML-BP) (n = 21) patients. Meanwhile, the comparative efficacy of three generations of TKIs in Ph+ ALL (n = 92) and CML-BP (n = 23) and the relationship between *ABL1* KD mutations and different TKI selection were analyzed.

Results

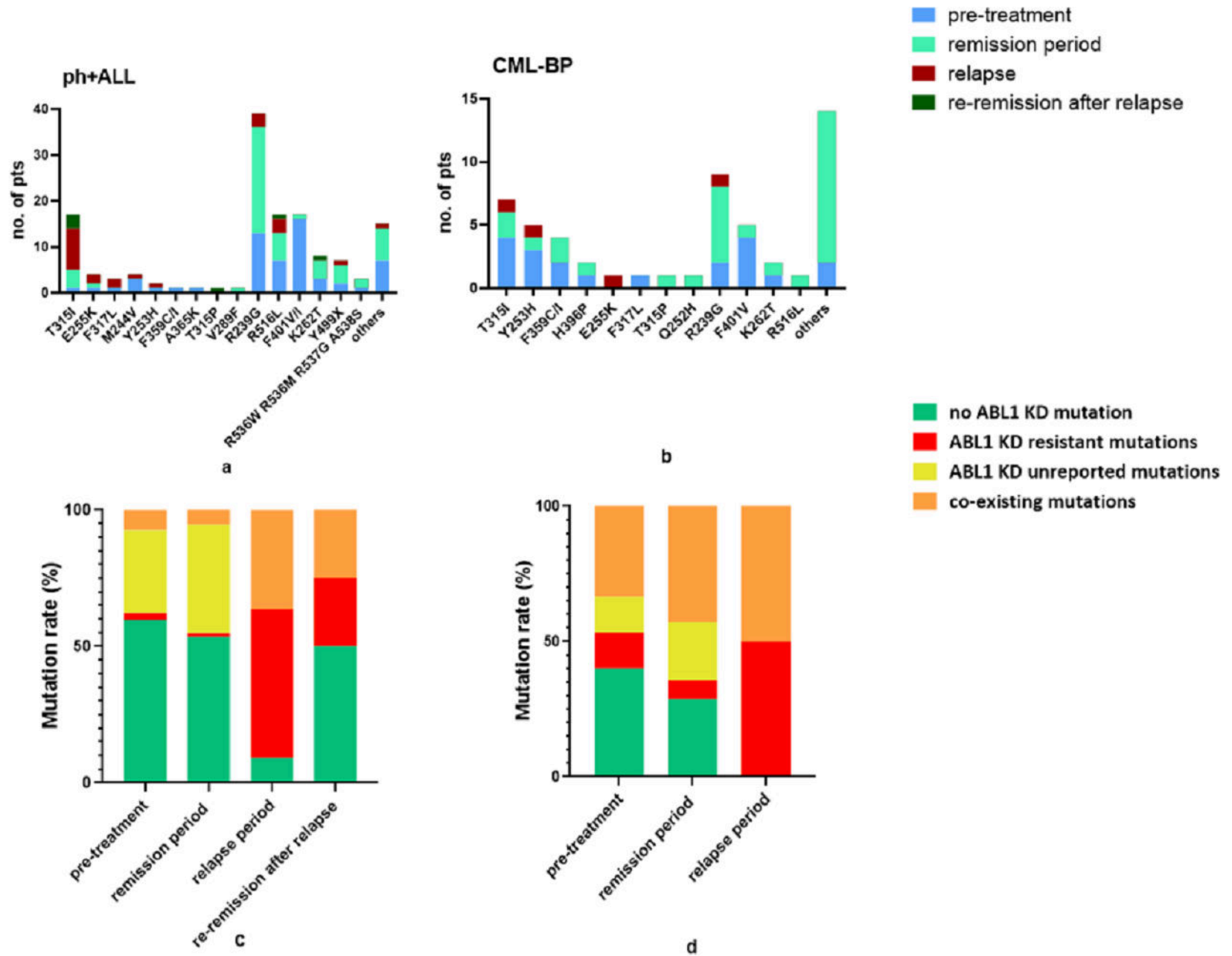
In Ph+ ALL patients, single *ABL1* KD unreported mutations were detected in 30.49% of patients before therapy and 39.73% in remission, which accounted for the highest proportion among other mutation types. Conversely, single *ABL1* KD resistant mutations were found to be the most prevalent (54.5%) in relapsed patients ($P < 0.0001$). Logistic analysis revealed that the presence of F401V/L in untreated Ph+ ALL patients was associated with a higher risk of relapse ($P < 0.1$). Furthermore, through analyzing patients who received TKI treatment, we observed that 3G TKIs like olverembatinib exhibited advantages in prognosis, including achieving deep molecular response, rapid remission reduction, and decreased relapse probability, for both newly diagnosed and relapsed Ph+ ALL patients. Notably, 3G TKIs not only demonstrated strong inhibition against the T315I mutation, as previously reported, but also displayed superior effectiveness against certain *ABL1* KD unreported mutations, such as R516L, K262T, and F401V. Similar trends were observed in CML-BP, although statistical significance was not reached likely due to the limited number of patients.

Conclusion

Overall, our findings indicate the prevalence and impact of *ABL1* KD mutations in Ph+ ALL and CML-BP patients, highlighting the necessity for effective therapies targeting these mutations. The promising outcomes observed with 3G TKIs suggest their potential as a treatment option for both newly diagnosed and relapsed Ph+ ALL patients, offering advantages in terms of molecular response depth, rapid remission, and reduced relapse risk. Further investigations are warranted to explore the clinical significance of unreported *ABL1* KD mutations and validate the effectiveness of 3G TKIs against them.

Disclosures No relevant conflicts of interest to declare.

<https://doi.org/10.1182/blood-2023-188208>



Distribution and relative frequency of ABL1 kinase domain mutations found in ph+ALL patients (a) and CML-BP patients (b). Dynamic change of BCR ABL KD mutations during disease stages in patients with ph+ ALL patients (c) and CML-BP (d) patients.

Figure 1