Clonal Hematopoiesis with Somatic Mutations in „AYA“ Generation of Patients With Chronic Myeloid Leukemia

INTRODUCTION

During chronic myeloid leukemia (CML) hematopoiesis, the myeloid lineage development is primarily impaired and untreated CML progresses to a terminal myeloid or lymphoid blast phase. Before introduction of tyrosine kinase inhibitors (TKIs) into the clinical practice, the higher age was a negative prognostic factor (Cortes et al. 2003). In contrast, in the current era of TKIs, it seems that younger patients with chronic phase of CML at age 15-39, defined by National Comprehensive Cancer Network (NCCN) guidelines as adolescents and young adults (AYA), have worse prognosis and response to TKIs. The clonal hematopoiesis with somatic mutations is an age-related phenomenon with a frequency around 10% for population older than 65 years in contrast to the population younger than 50 years with frequency of 1%. In recent years, mutations in genes involved in epigenetic modification and RNA splicing, which are recurrently mutated in myeloid neoplasms have been highly reported and seem to represent a premalignant condition (Branford et al. 2019; Kim et al. 2017). However, except for mutations in the kinase domain of BCR-ABL1, very little is known about the genomic landscape of CML AYAs and their potential effect on resistance to the TKI treatment and relapses.

AIM

To determine, whether the worse prognosis of CML AYAs, resulting in the therapy failure and disease progression, is associated with the clonal hematopoiesis with somatic mutations.

RESULTS

Almost a half (9/21) of AYAs that in follow up failed on TKIs harbored somatic mutations at the time of diagnosis

At the time of diagnosis, somatic mutations were identified in AXL1 (n=3), CSF1R (n=1), TET2 (n=1), DNMT3A (n=2), ATM (n=1), and SRPR (n=1) in 9/21 AYAs who subsequently failed on TKI treatment. Overall, 5 missense, 3 frameshift mutations and one nonsense mutation were detected. According to VarSome database (Kopanos et al. 2018), detected mutations in AXL1, RUNX1, DNMT3A were reported as pathogenic/likely pathogenic. Mutation R863Q in DNMT3A gene lies within the SAM-dependent MTase C5-type domain of the Dnmt3a protein and probably in a loss of function.

The detected mutations were categorized into mutation patterns according their presence at the diagnosis and/or at the time of TKI failure.

AXL1 was the most frequently mutated gene at the time of diagnosis

Four patients harbored a mutation in AXL1 gene at the time of diagnosis. All the mutations in AXL1 gene involved in epigenetic modification, were found in exon 12. In patient #6, G645delinsG98W was found at the diagnosis and on the 3rd line nilotinib treatment. In patient #10, nonsense mutation E775X was confirmed at the time of TKI failure and also at the allo-HSCT relapse. Another AXL1 mutation, S795delinsL5, was found in a patient #1 only at diagnosis. In patient #19, AXL1 mutation T1372delinsT6Ts was found at both time points.

Mutation D198N in RUNX1 gene in T315I-BCR-ABL1-mutated clone was responsible for the resistance to TKIs and recurrent relapses after allo-HSCTs

The patient 25 years old at the time of diagnosis relapsed after 3rd allo-HSCTs due to Ph+ clone with a quick development of D198N mutation in RUNX1 and T315I in BCR-ABL1 kinase domain on imatinib therapy first line. The clone persisted after 2nd allo-HSCT even though the patient was in major molecular response (MMR). After ponatinib start, the patient achieved undetectable levels of BCR-ABL1, but subsequently relapsed to blast phase in CNS followed by the blast phase relapse in bone marrow. After the third allo-HSCT, patient quickly relapsed to blast phase and died.

CONCLUSION

The preliminary data of this work outlined that somatic mutations in the myeloid genes are frequently found in CML AYAs, who failed on the TKI or relapsed after allo-HSCT, alone or together with mutated BCR-ABL1. The most frequently mutated gene was AXL1, which is in line with the work by Ernst et al. (2018) even though on younger patients including children. Despite the clonal hematopoiesis with somatic mutations is considered as age-related phenomenon, in AYA CML patients, it may represent a critical problem in achieving sustained response on solo TKI therapy, or even worse, it may result in higher risk of therapy failure and disease progression.

REFERENCES


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