



## The 65th ASH Annual Meeting Abstracts

## POSTER ABSTRACTS

## 632. CHRONIC MYELOID LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

**Somatic Mutations in Cancer-Related Genes Were Observed More Frequently in AYA CML Patients Compared to Elderly at Diagnosis, Whereas the Frequency Was Markedly Higher in Elderly Patients during TKI Treatment**

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**INTRODUCTION** Several works showed that patients with chronic myeloid leukemia (CML) diagnosed at the age of 18 to 39 years (adolescent and young adults, AYAs), had a worse outcome of tyrosine kinase inhibitors (TKI) therapy compared to elderly patients. Only limited data on the molecular background differing AYA from the other age groups are available.

**OBJECTIVES** To characterize the somatic mutation landscape of AYA CML patients in chronic phase at the time of diagnosis and follow-up in comparison to pediatric and elderly patients, and to follow their clonal evolution. Ph-positive acute lymphoblastic leukemia (Ph+ ALL) patients were included for comparison.

**METHODS** Samples from the time of diagnosis (CML children N=18; AYA N=69; elderly N=70; Ph+ ALL children N=32, AYA N=13, elderly N=39) and TKI treatment follow-up (CML AYA N=69, elderly N=70) were analyzed with custom panel (22 whole genes, 40 selected exons). To follow the clonal evolution vital cells available from 10 CML patients were FACS sorted into populations of neutrophils, monocytes, T- and B-lymphocytes. Genomic *BCR::ABL1* (g *BCR::ABL1*) and mutations were quantified using ddPCR in the sorted cells.

**RESULTS** At the time of diagnosis, a slightly higher frequency of somatic mutations was detected in AYA CML patients (28%, 19/69) compared to elderly (20%, 14/70) and children (11%, 2/18). The similar trend with markedly higher differences was observed in Ph+ ALL patients (62% 8/13 of AYA, 31% 12/39 of elderly, 22% 7/32 of pediatric). The most frequently mutated genes in AYA and elderly CML patients were identically *ASXL1*, *DNMT3A*, and *TET2*. Other mutated genes in AYA were *FBXW7*, *IDH2*, *IKZF1*, *PHF6* and *KDM6A*, *SETD2*, *SF3B1* in elderly. Considering the treatment response, a higher number of mutations at diagnosis were found in the AYA patients that responded optimally in follow-up (21%, 7/33) than in elderly 4% (1/26) and a slightly higher frequency of mutations in AYA patients who later failed on TKI (35%, 8/23) than in elderly 30% (13/43). In contrary, the frequency of acquired mutations or persisted mutations from diagnosis detected during TKI therapy was higher in elderly that failed on TKI therapy (67%, 29/43) than in AYA (52%, 12/23). The treatment failure was associated with *de novo* mutations in *ABL1*, *RUNX1*, *TET2*, *ASXL1* in AYA and elderly CML patients, and in addition in *IKZF1*, and in *DNMT3A*, *WT1*, *JAK2*, respectively.

Sorted cells were analyzed from the time of optimal response in 7 CML patients (+ diagnostic sample of 2 patients) with mutated *ASXL1* in 6 patients, *FBXW7* in 1 patient, *DNMT3A* in 1 patient and *IDH2* in 1 patient. Samples from the time of therapy failure were available for sorting of 3 patients (+ diagnostic sample of 1 patient). All mutations were detected in g *BCR::ABL1* positive neutrophils and monocytes. The g *BCR::ABL1* levels matched exactly with the levels of mutations except for 1 patient with *ASXL1*-mutated subclone (VAF 5%), which was found in g *BCR::ABL1* positive cells. Similar data were found in patients with therapy failure. However, in one patient with secondary failure, the *ASXL1* mutation detected at diagnosis disappeared. In all 10 CML patients, g *BCR::ABL1* and mutations were not detected in T- and B- lymphocytes under the therapy. In diagnostic samples some g *BCR::ABL1* and mutations positive T- and B- lymphocytes were found, but the levels were 3-4 log lower compared to levels in neutrophils and monocytes, which likely correspond to the contamination (purity check was done after sorting) than to the presence of a very small subset of physiological lymphoid cells.

**CONCLUSIONS** Of all age groups, AYAs had the highest number of mutations detected at the time of diagnosis with differences in the spectrum between CML and Ph+ ALL. A markedly higher *de novo* acquisition of mutations was observed in elderly CML patients during TKI treatment. Moreover, therapy failures were observed more frequently in elderly than in AYA CML patients. Clonal analysis of 10 CML patients outlined that myeloid, but not lymphoid stem/progenitor cells were mutated.

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**Disclosures** No relevant conflicts of interest to declare.

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