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POSTER ABSTRACTS

632.CHRONIC MYELOID LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Whole Genome and Transcriptome Sequencing of 21 Paired Chronic and Blast Phase CML Cases: Acquisition of Genomic Alterations, Changes in the Transcriptomic Profiles and Occurrence of B-Cell Receptor Rearrangements

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Background: Since the introduction of tyrosine kinase inhibitor therapy survival has substantially improved in CML. However, a subset of patients become resistant and progress to blast phase. Still the underlying genomic changes are not completely understood.
Cohort & Methods: We studied 21 CML patients with paired sample material available from diagnosis in chronic phase (CP) and from blast phase (BP). All patients received a tyrosine kinase inhibitor starting at diagnosis of CML CP. Samples were analyzed by cytomorphology, chromosome banding analysis, WGS (100x, 2x151bp) and WTS (50 Mio reads, 2x101bp). B-cell receptor (BCR) rearrangements were analyzed with MiXCR software. The transcriptomic phenotype (TP) of each CP and BP sample was estimated by mapping their profiles to representative cases diagnosed with B-ALL, T-ALL, MDS, CMML, AML and CML CP.
Results: The median time between diagnosis of CP and BP was 14.7 months (range: 4.7 - 137 months). While 18/21 CML in CP showed a TP corresponding to CML CP, one case each showed a TP corresponding to CMML, AML and B-ALL, respectively, although bone marrow blast counts were 6.5%, 5.5% and 5.5%, respectively. Of note, the case with the CMML-TP harbored a p190 *BCR*:: *ABL1* isoform and also resembled CMML in bone marrow morphology. These three cases progressed to BP after 5.8, 5.3, and 8.9 months. The TP in BP corresponded to B-ALL in 13 cases, while 4, 3, and 1 case showed an AML-, CML CP- and MDS-TP, respectively (figure). In CP recurrent genomic alterations in addition to the *BCR*:: *ABL1* fusion were mutations in *ASXL1* (n=5), *DNMT3A*, *TET2*, *RUNX1*, and *MGA* (2 cases each). In BP the genomic landscape was more complex. Additional genetic alterations compared to CP were detected in all cases. Recurrently gained mutations in BP were mutations in *WT1*, *BCOR*, and *SETD2* (2 cases each). The gain of copy number alterations (CNA) was more frequent. Recurrent CNA were: loss 9p (n=6), gain Ph-chromosome (n=4), loss 7q (n=3), gain 21q (n=3), gain 1q, loss 3q, gain 8q, loss 12p, and loss 13q in 2 patients each. Only three balanced structural variants were gained: a *MECOM*-, a *NUP98*:: *HHEX*- and a *KMT2A*:: *MLLT3*-rearrangement. Further, in 11/21 BP resistance mutations within the *BCR*:: *ABL1* kinase domain were detected. The variant allele frequency (VAF) of *RUNX1* mutations increased in BP in both cases with *RUNX1* mutation present in CP (5% to 42%, time to BP: 4.7 months; 8% to 59%, time to BP: 11.7 months). *DNMT3A* and *MGA* mutations were about stable (VAF CP/BP: *DNMT3A*: 48%/37%, 33%/46%; *MGA*: 52%/36%, 40%/52%), while *TET2* mutations were stable in one case (46%/49%) and decreased in the second (57%/27%). *ASXL1* mutations were stable in 2 cases with an AML-TP in BP and lost in 3/5 cases with a B-ALL-TP in BP. BP with a lymphoid TP differed substantially with respect to the genomic profile from BP with myeloid TP. WTS data revealed a clonal BCR rearrangement in 8/13 BP with B-ALL-TP, of which 4 rearrangements are predicted to be productive. Further, *CDKN2A/B* deletions, *IKZF1* deletions, and *SETD2* mutations were only found in BP with B-ALL-TP. Thus, CML in BP with a B-ALL-TP showed a genomic landscape similar to B-ALL with *BCR*:: *ABL1*-rearrangement. In contrast CML BP cases with an AML-TP (n=4) had gained either rearrangements typically found in AML such as a *KMT2A*:: *MLLT3* rearrangement and a *MECOM* rearrangement or acquired mutations in *RUNX1*, *BCOR* and *WT1*, or a CN-LOH 11p in combination with a *WT1* VAF increase from 51% to 94%. Cases showing still a CML CP-TP (n=3) in BP acquired rather few additional genetic abnormalities (mutations in *BCOR*, *WT1*, *CTCF*; *NUP98*:: *HHEX*-rearrangement, gain of Ph-chromosome, loss of 11p, 17q), which were more myeloid in appearance.
Conclusions: 1) Extensive genetic profiling indicated a substantial clonal evolution in the progression from CP to BP CML including loss of *ASXL1* mutations, expansion of *RUNX1* mutated clones, multiple CNA, and the frequent acquisition of a BCR rearrangement in BP with a transcriptomic phenotype resembling B-ALL. 2) A subset of CML cases in CP already showed

a transcriptomic phenotype resembling acute leukemia indicating a rapid progression to BP. 3) The presence of a *RUNX1* mutated subclone or a clonal BCR rearrangement seem to represent a warning signal in CML CP. 4) The prognostic validity of an extended genetic profiling including *ASXL1*, *RUNX1*, BCR rearrangement, and transcriptional signature in CML CP needs to be assessed in forthcoming prospective studies.

Disclosures Haferlach: *MLL Munich Leukemia Laboratory:* Current Employment, Other: Equity Ownership. **Walter:** *MLL Munich Leukemia Laboratory:* Current Employment. **Mueller:** *MLL Munich Leukemia Laboratory:* Current Employment. **Huber:** *MLL Munich Leukemia Laboratory:* Current Employment. **Baer:** *MLL Munich Leukemia Laboratory:* Current Employment. **Hutter:** *MLL Munich Leukemia Laboratory:* Current Employment. **Meggendorfer:** *MLL Munich Leukemia Laboratory:* Current Employment. **Hoermann:** *MLL Munich Leukemia Laboratory:* Current Employment. **Kern:** *MLL Munich Leukemia Laboratory:* Current Employment, Other: Equity Ownership. **Haferlach:** *MLL Munich Leukemia Laboratory:* Current Employment, Other: Equity Ownership.

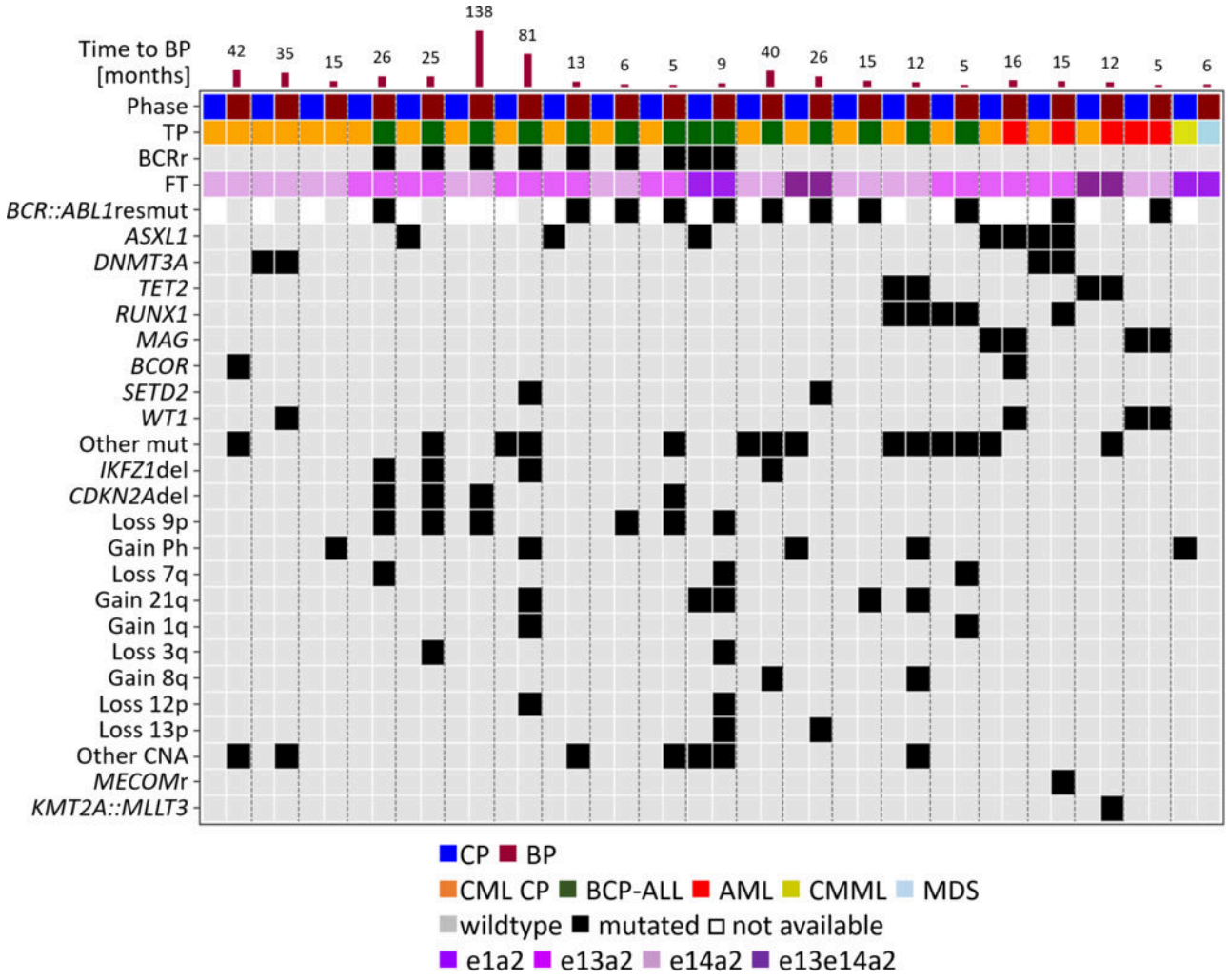

Figure: Molecular characterization of CML patients. Illustration of all 21 patients separated by dotted lines, each column represents one phase of each patient. CP: chronic phase; BP: blast phase; TP: transcriptomic phenotype; r: rearrangement; FT: fusion transcript; *BCR::ABL1*resmut: *BCR::ABL1* resistance mutation; mut: mutation; del: deletion; Ph: Philadelphia chromosome; CNA: copy number alteration

Figure 1

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