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Blood 142 (2023) 2978–2979

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

618.ACUTE LYMPHOBLASTIC LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

The Relapse Mechanisms and Genomic Landscape Differ in *KMT2A*-r Pediatric Leukemia in Relation to Relapse Time

Louise Ahlgren, PhD[1], *Mattias Pilheden, PhD*[1], *Helena Sturesson, PhD*[1], *Varsha Singh, PhD*[1], *Qirui Zhang, PhD*[1], *Michael Walsh, MD*[2], *Guangchun Song*[2], *Anders Castor*[3], *Cornelis Jan Pronk, MD PhD*[3], *Pauline Schneider*[4], *Ronald W. Stam, PhD*[4], *Gisela Barbany*[5], *Katja Pokrovskaja Tamm, PhD*[6], *Jonas Abrahamsson*[7], *Linda Fogelstrand, MD PhD*[8], *Olli Lohi, MDPhD*[9], *Jing Ma, PhD*[2], *Jinghui Zhang, PhD*[10], *Anna K. Hagstroem-Andersson, PhD*[1]

[1] Department of Laboratory Medicine, Division of Clinical Genetics, Lund University, Lund, Sweden
[2] Department of Pathology, St. Jude Children's Research Hospital, Memphis, TN
[3] Childhood Cancer Center, Skåne University Hospital, Lund, Sweden
[4] Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands
[5] Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden
[6] Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden
[7] Institution for Clinical Sciences, Department of Pediatrics, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, Gothenburg, Sweden
[8] Department of Clinical Chemistry, Sahlgrenska University, Gothenburg, Sweden
[9] Tampere Center for Child, Adolescent and Maternal Health Research, Faculty of Medicine and Health Technology, Tampere University and Tays Cancer Center, Tampere University Hospital, Tampere, Finland
[10] Department of Computational Biology, St. Jude Children's Research Hospital, Memphis, TN

The genomic landscape and mechanisms driving relapse in *KMT2A*-rearranged (*KMT2A*-r) infant and childhood acute lymphoblastic (ALL) and acute myeloid leukemia (AML) are not completely understood. We therefore studied 36 *KMT2A*-r ALL (n=19) and AML (n=17) patients of which 25 relapsed and 11 remained in remission. Twenty diagnose-relapse-germline trios and 5 multiple relapse samples were analyzed by whole genome (WGS) and whole exome sequencing (WES) and 30 patients longitudinally by using patient-specific mutations identified by WGS/WES, including the *KMT2A*-r (average coverage 3300X). The mutational burden increased from diagnosis to relapse and relapse evolved through branching evolution. Relapse was seeded by multiple diagnostic clones in 56%, by a single sweeping clone detected at diagnosis in 22%, and by a single sweeping clone not detected at diagnosis in 22%. Notably, the evolutionary patterns correlated to relapse time, where multiple diagnostic clones seeding relapse were connected to an earlier relapse with all very early relapse ALL (3/3, relapse <9 months from diagnosis) and half of the early AML relapse showing this pattern (2/4, relapse <1 year in complete remission, CR1). By contrast, later relapse was connected to a sweeping clone at relapse with 67% of early relapse ALL (>9 months from diagnosis) and 40% of late relapse AML (>1 year in CR1) showing this pattern.

Pathway analysis showed that cell cycle genes, glucocorticoid signalling, purine metabolism, mismatch repair, and B-cell differentiation, were enriched in early relapse ALL (83%, 5/6) and included *TP53*, *CREBBP*, *NT5C2 PMS2*, *PRPS2*, *NR3C1*, *IKZF1*, with none of the very early relapse infant ALL harboring such alterations (n=4). Further, *TP53* and *IKZF1*alterationsco-occurred (n=4/4). These results were validated in public data sets of 98 *KMT2A*-r ALL infants (n=84) and children (n=14) at diagnosis and relapse (n=24) and showed that 50% of early relapse ALL, and none of the 8 very early relapse ALL, had such alterations. Ultra-deep sequencing did not detect the *CREBBP*, *NT5C2*, *PRPS2*or *TP53* mutations at diagnosis and manual inspection of the WGS reads failed to detect the *PMS2* and *NR3C1* deletions. In AML, *TP53* and *CCND3* alterations were maintained, and gain of *WT1* was seen in late relapse AML.

Signalling mutations were the most common type of mutations at diagnosis (64%) and relapse (56%) and the frequency was similar in patients that remained in remission and in those that relapsed (55% versus 60%). One infant ALL and four AML patients had multiple relapses, allowing us to study how the genetic landscape evolved across consecutive relapses. This showed a stepwise replacement of clones during treatment in agreement with a fitter clone that evolves under chemotherapeutic selective pressure.

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Longitudinal analysis allowed sensitive detection of residual leukemia cells and showed that the relapse clone could be detected at diagnosis in 64% of patients. Further, infants with >10% of molecularly detectable leukemia cells after induction therapy, had a high risk of a very early relapse. Ultra-deep sequencing allowed detection of the relapse clone up to 4 months before relapse. In 11 of the 30 patients (3 remission and 8 relapse), low-frequency *KMT2A*-fusion positive leukemic cells were found at remission outside of the MRD time points. Our longitudinal data also provided unique insights into clonal response to treatment by showing that 1) a change in therapy can favour the eradication of one clone and expansion of another, 2) a clone that initially was the most sensitive clone to therapy, was the one that eventually caused relapse, and 3), a diagnostic clone can be undetectable for a long time before expanding to cause relapse, suggesting that molecular monitoring with personal mutations is a powerful tool to follow response to therapy.
These results provide new biological insights into the relapse mechanisms in *KMT2A*-r leukemia. The data shows different clonal evolution patters depending on when in time the patient relapsed, with very early relapse ALL being seeded by multiple diagnostic subclones and a paucity of acquired genetic alterations at relapse. By contrast, early relapse ALL was characterized by a single diagnostic clone seeding relapse by a clonal sweep along with acquired mutations in chemoresistance-associated genes. To validate and extend these findings, we are currently analyzing 11 additional infant relapse samples with WGS.

Disclosures No relevant conflicts of interest to declare.

https://doi.org/10.1182/blood-2023-185044

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