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POSTER ABSTRACTS

617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Heterogeneous Gene Fusion Transcripts Found in t(7;12)(q36;p13) Acute Myeloid Leukemia but with Similar Gene Expression Profile

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Cytogenetic aberrations are often involved in acute myeloid leukemia (AML) and can serve as diagnostic markers, prognosis predictors and impact the choice of therapy. A translocation t(7;12)(q36;p13) is reported in up to 20-30% of AML patients typically diagnosed before 24 months of age (Beverloo, Panagopoulos et al. 2001, Cancer Res 61(14): 5374-5377). However, in a retrospective survey of the Nordic Organization of Pediatric Hematology and Oncology (NOPHO) registry, only 4% of reported AML diagnosed before 24 months of age had t(7;12) (Espersen, Noren-Nystrom et al. 2018, Genes Chromosomes Cancer 57(7): 359-365). The t(7;12) is difficult to identify with conventional karyotyping, why the true frequency of t(7;12) may be underestimated. Similarly, the reported prognosis for t(7;12) patients has varied ranging from good (Espersen, Noren-Nystrom et al. 2018) to dismal (von Bergh, van Drunen et al. 2006, Genes Chromosomes Cancer 45(8): 731-739). The translocation has been reported to give rise to an in-frame fusion transcript, *MNX1::ETV6*. However, detection of this fusion is reported only in 50% of cases in contrast to high expression of *MNX1* in 100% (von Bergh, van Drunen et al. 2006). The aim of this study was to determine the frequency of the t(7;12) in pediatric AML patients in the NOPHO AML-2004/2012 protocols, their event-free and overall survival and to investigate the presence of additional genetic alterations.

Patients in Sweden, Denmark, or Iceland between 2004 to 2020 diagnosed with AML before 2 years of age that had not been reported with a recurrent genetic aberration plus all patients diagnosed with t(7;12) AML were identified. Bone marrow, or peripheral blood samples from patients were retrieved from the NOPHO biobank. This cohort constituted 86% (31 out of 36) of all patients that fulfilled these criteria. In total 89 AML patients were diagnosed before 2 years of age. The t(7;12) AML cases were identified by screening for high expression of *MNX1* and presence of fusion transcripts using whole transcriptome sequencing (WTS). Whole genome sequencing (WGS) was done to identify chromosomal rearrangements, and translocation breakpoints.

At diagnosis, four patients were diagnosed with t(7;12). A central karyotype review of all patients reported two additional cases. No further cases were identified using WTS. Thus, the frequency of t(7;12) AML was 7% (6 out of 89) and for patients diagnosed before 12 months of age 11% (5 out of 47). In total 12 cases with t(7;12) were identified in the complete NOPHO registry but only 11 patients received treatment according to NOPHO protocol. The relapse rate was 54% (6 out of 11). All relapse cases underwent allogeneic hematopoietic stem cell (HSC) transplantation in complete remission two (CR2), and their overall survival (OS) was 83% (5 out of 6). Hence OS for all t(7;12) patients treated according to the NOPHO2004 and NOPHO2012 protocols was 91% (10 out of 11).

Analysis of WTS data showed similar gene expression profile between our t(7;12) cases and t(7;12) cases retrieved from the TARGET database. Genes that were typically overexpressed in all t(7;12) AML were, *MNX1, MNX1-AS1, MNX1-AS2, LIN28B, BAMBI, MAF, CRISP3, EDIL3, CTTNBP2, KRT72*, and *AGR2*, where *MNX1* seems to be uniquely expressed in this type of

leukemia (Nilsson et al. 2022, Int J Cancer 151(5): 770-782). Analysis of fusion transcripts showed presence of *MNX1::ETV6* in just one case. The remaining cases instead showed presence of other fusion transcripts involving *ETV6*, *NOM1::ETV6, ETV6::NOM1, ETV6::LMBR1 and ETV6::BMAL2*. WGS verified a fusion between NOM1 and ETV6 in 3 cases. The patient with *ETV6::BMAL2* showed that 16 Mb of chromosome 12 was inserted into chromosome 7 placing a large part of ETV6 near MNX1. The fusion transcript *ETV6::BMAL2* is the product of what remains on chromosome 12.
In conclusion, frequency of t(7;12) AML in the NOPHO treatment cohort was approximately 7%, with 54% relapse rate, but most patients were salvaged by HSCT in CR2. Heterogeneous gene fusion transcripts were identified in this subgroup of AML where *ETV6::NOM1* was most frequent. However, all cases showed similar gene expression signatures which underlines that the leukemia driving event is ectopic expression of *MNX1* (Waraky, A., 2023, Haematologica, DOI: 10.3324/haematol.2022.282255) and should therefore be the defining classifying criteria of this type of AML.

Disclosures No relevant conflicts of interest to declare.

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