The incidence of chromothripsis in childhood B-cell precursor acute lymphoblastic leukemia

Zuzanna Urbańska [1]*

Supervisor: MD, PhD Wojciech Młynarski [1]
Assistant supervisor: MD, PhD Agata Pastorczak [1]

1) Department of Pediatrics, Oncology and Hematology, Medical University of Lodz; Lodz

INTRODUCTION

Despite cure rates approaching 90%, chemoresistance and relapse of the disease make BCP-ALL the most common cause of death due to malignancy in children. Chromothripsis is a form of genomic instability leading to massive de novo structural chromosome rearrangements within one-step catastrophic event. It occurs in 2-3% of all malignancies and is associated with poor prognosis. Genetic background and molecular consequences of this phenomenon are poorly understood in BCP-ALL except for intrachromosomal amplification of chromosome 21 (iAmp21).

AIM OF THE STUDY

The assessment of the incidence of the chromothripsis in pediatric BCP-ALL depending on the stage of the disease.

MATERIAL AND METHODS

The study included a cohort of pediatric patients in the age range within 0-18 years, with a diagnosis (n=438) and recurrence (n=138) of BCP-ALL. Identification of chromothripsis was performed using the Korbel criteria (oscillating copy number profile, which requires detection of at least 10 copy number changes on a given chromosome with only two or three simultaneous copy number states). The isolated DNA from blasts from the day of diagnosis and/or relapse were analyzed using CytoScan HD microarrays (Applied Biosystems, Thermo Fisher Scientific, Waltham, MA).

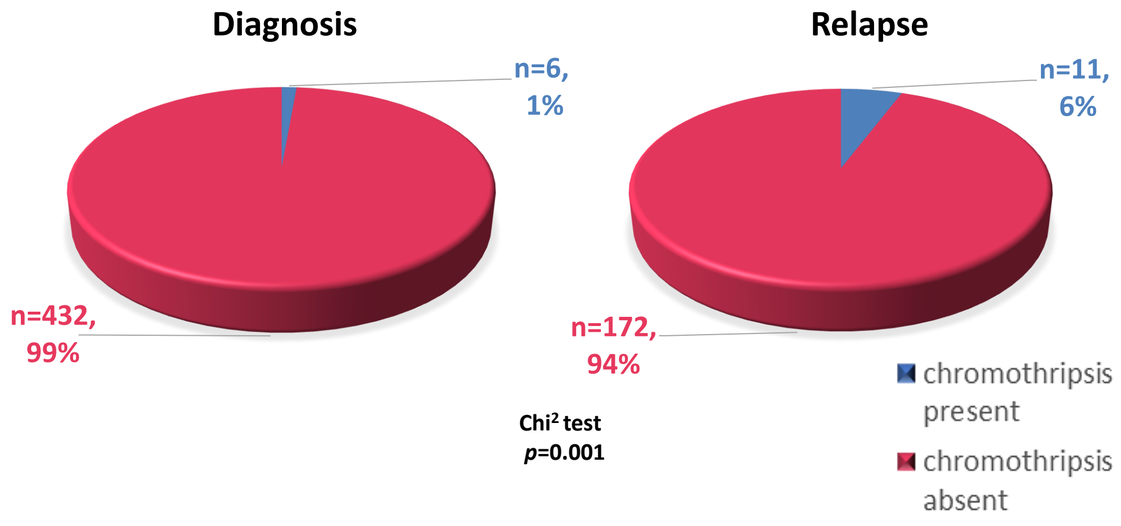

Figure 1.
The frequency of chromothripsis at diagnosis and at relapse of chlidhood BCP-ALL.

RESULTS

As a preliminary analysis, we explored chromothripsis patterns in the cohort of 438 (n=438) pediatric BCP-ALL samples collected at diagnosis This phenomenon was found in n=6 (6/438; 1.5%) patients. All of them presented a positive result for minimal residual disease (MRD) at day 15 and/or 33 day of the treatment and the analysis of co-existing aberrations revealed somatic defects in tumor suppressor genes such as *RB1* and *TP53*. Based on these results, we investigated the frequency of chromothripsis in patients who experienced a relapse of the disease. The frequency of chromothripsis depending of the stage of the disease is presented on **Figure 1**. We identified chromothripsis in n=11 (11/183; 6%) relapse samples. Among them, matched samples i.e. from diagnosis and relapse were available in 6 patients (6/11; 54%). In 4 (4/6; 66,7%) cases chromothripsis was identified in both time-points, but in two children (2/6; 33,3%) it was detected in relapse only. The example of chromotrhiptic pattern is presented on the **Figure 2**. The most frequently affected chromosome by chromothripsis were the following ones: chr. 21, chr. 7 (n=2/11), chr. 9 (n=2/11), chr. 15 (n=1), chr. 17 (n=1), and chr. 19 (n=1). In one patient chromotrhripsis was identified on two chromosomes: chr. 7 and chr. 9.

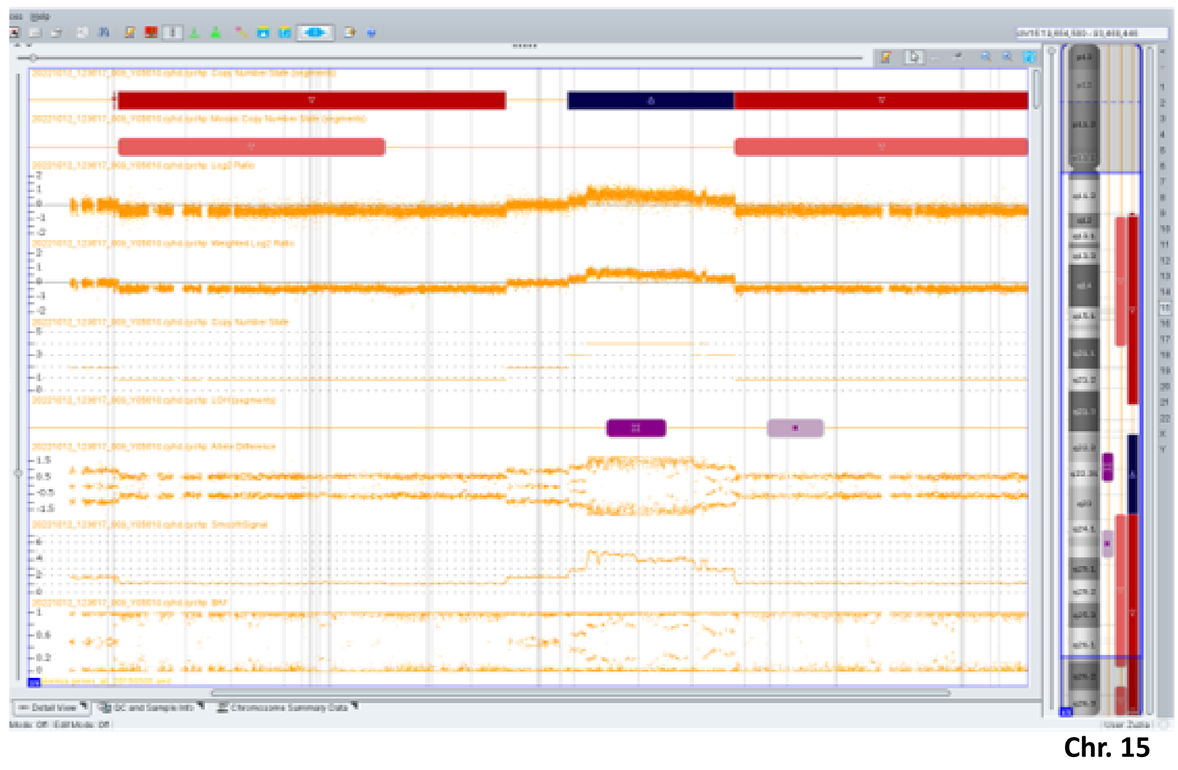

Figure 2.
The example of the chromothripsis pattern within *q*-arm of chromosome 15

CONCLUSIONS

The incidence of chromothripsis at BCP-ALL relapse is higher as compared to primary diagnosis (p=0.01), which may indicate its association with chemoresistance of tumor cells. Further characterization of the consequences of chromothripsis in the leukemic genome needs further studies.

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