Loss of Heterozygosity in the Short Tandem Repeat (STR) Loci Found in Tumor DNA of *De Novo*-Diagnosed ALL Patients as a Factor Predicting Poor Outcome

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Introduction

Loss of heterozygosity (LOH) has been described for many malignancies, including leukemia. We previously noted that LOH at STR loci is especially common in patients with recurrent ALL. The question of whether the LOH established for de novo-diagnosed ALL can be used as a prognostic factor for a possible poor clinical outcome has not yet been answered.

OBJECTIVE: To identify LOH in the blast cells of the patients with ALL at diagnosis and to analyze therapy outcomes relative to patients without LOH.

Methods

This study includes an analysis of the STR profiles of the DNA of tumor cells from a cohort of 47 patients with *de novo*-diagnosed Ph-negative ALL undergoing treatment according to the "RALL-2016" regimen at the National Research Center for Hematology (Moscow, Russia). Inclusion criteria:18–55 years old, intermediate risk group without MLL translocation t(4;11)(q21;q23). Exclusion criteria: patients older than 55 years, MLL translocation t(4;11)(q21;q23), and pre-treatment.

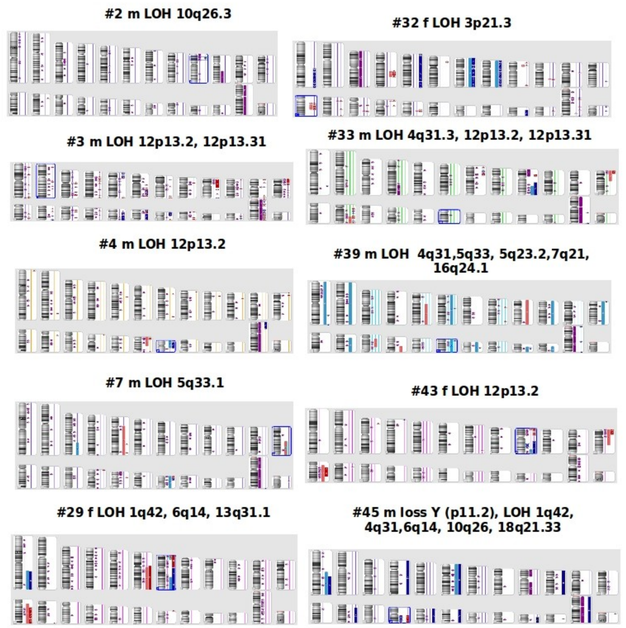
DNA was isolated from patient bone marrow samples taken at diagnosis. Control DNA samples were taken from the blood of patients in complete remission and/or from the buccal swab. STR profiles were assessed by PCR with COrDIS Plus multiplex kit for amplification of 19 polymorphic STR-markers and amelogenin loci (Gordiz Ltd, Russia).

Multivariate survival analysis was used to assess the independent impact of the LOH as a risk factor. Overall survival (OS) was chosen as a primary endpoint. Patients with the LOH at the short arm of 12 chromosome (12pLOH) are excluded from the risk group because 12p LOH is not associated with worse outcome according to many publications.

Results

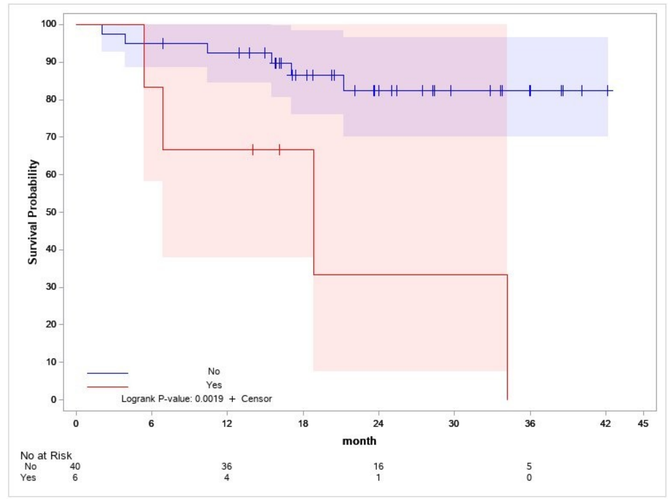
Ten patients were found with LOH in the certain STR loci (21%) out of 47. 12p LOH was detected in 4 patients. OS of patients with other LOH was significantly lower than for patients without LOH (HR=6.02 (95% CI: 1.66–21.78), p=0.0019).

Figure #1 *Chromosomal microarray (CMA) karyoview for 10 patients with detected LOH in STR loci*



LOH in STR loci were confirmed by CMA as patterns of deletions (red bars), duplications (blue bars) and copy-neutral LOH (purple bars) of big chromosomal areas or entire arm of chromosome.

Figure #2 *Overall survival estimates for stable **STR-profile** (blue line) **and LOH** (red line) **patients***



Conclusions

We have found a statistically significant association of clinical failures with the LOH in STR loci (except 12p LOH) measured at the onset of ALL.

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Bibliography

1. Xu X, Bryke C, Sukhanova M, et al. Assessing copy number abnormalities and copy-neutral loss-of-heterozygosity across the genome as best practice in diagnostic evaluation of acute myeloid leukemia: An evidence-based review from the cancer genomics consortium (CGC) myeloid neoplasms working group. Cancer Genet. 2018;228-229:218-235. doi:10.1016/j.cancergen.2018.07.005
2. Takeuchi, S., Tsukasaki, K., Bartram, C. et al. Long-term study of the clinical significance of loss of heterozygosity in childhood acute lymphoblastic leukemia. Leukemia 17, 149–154 (2003). https://doi.org/10.1038/sj.leu.2402727
3. Kawashima-Goto S, Imamura T, Seki M, et al. Identification of a homozygous JAK3 V674A mutation caused by acquired uniparental disomy in a relapsed early T-cell precursor ALL patient. Int J Hematol. 2015;101(4):411-416. doi:10.1007/s12185-014-1711-y