



Loss of Heterozygosity in STR Loci Found in Tumor DNA of De Novo Diagnosed ALL Patients as a Factor Predicting Poor

Outcome for B-ALL but not for T-ALL patients.

Natalya Risinskaya¹, Olga Gavrilina¹, Julia Chabaeva¹, Anna Yushkova¹, Yana Kozhevnikova², Valeriya Kovaleva², Sergey Kulikov¹, Hunan Julhakyan¹, Andrey Sudarikov¹, Elena Parovichnikova¹

¹National Research Center for Hematology, Moscow, Russia, ²School of Medicine, Lomonosov Moscow State University, Moscow, Russia



Background

Genetic instability of tumor cells can lead to a change in the profile of short tandem repeats (STR) of the tumor relative to the STR profile of healthy cells of the patient. Loss of heterozygosity or allelic imbalance in STR loci confirms the chromosomal aberrations revealed by standard cytogenetic analysis in chromosomes containing this STR locus: deletions, monosomies, duplications, and the appearance of isochromosomes [1,2]. However, in some patients, the loss of heterozygosity (LOH) is also observed with a normal tumor karyotype [3]. Our objective was to evaluate correlations between the loss of heterozygosity in blast cells of de novo diagnosed ALL patients and chromosomal aberrations revealed by standard cytogenetic analysis, as well as to verify hidden abnormalities in the case of discrepancies between cytogenetic data and molecular analysis of the STR profile of the tumor.

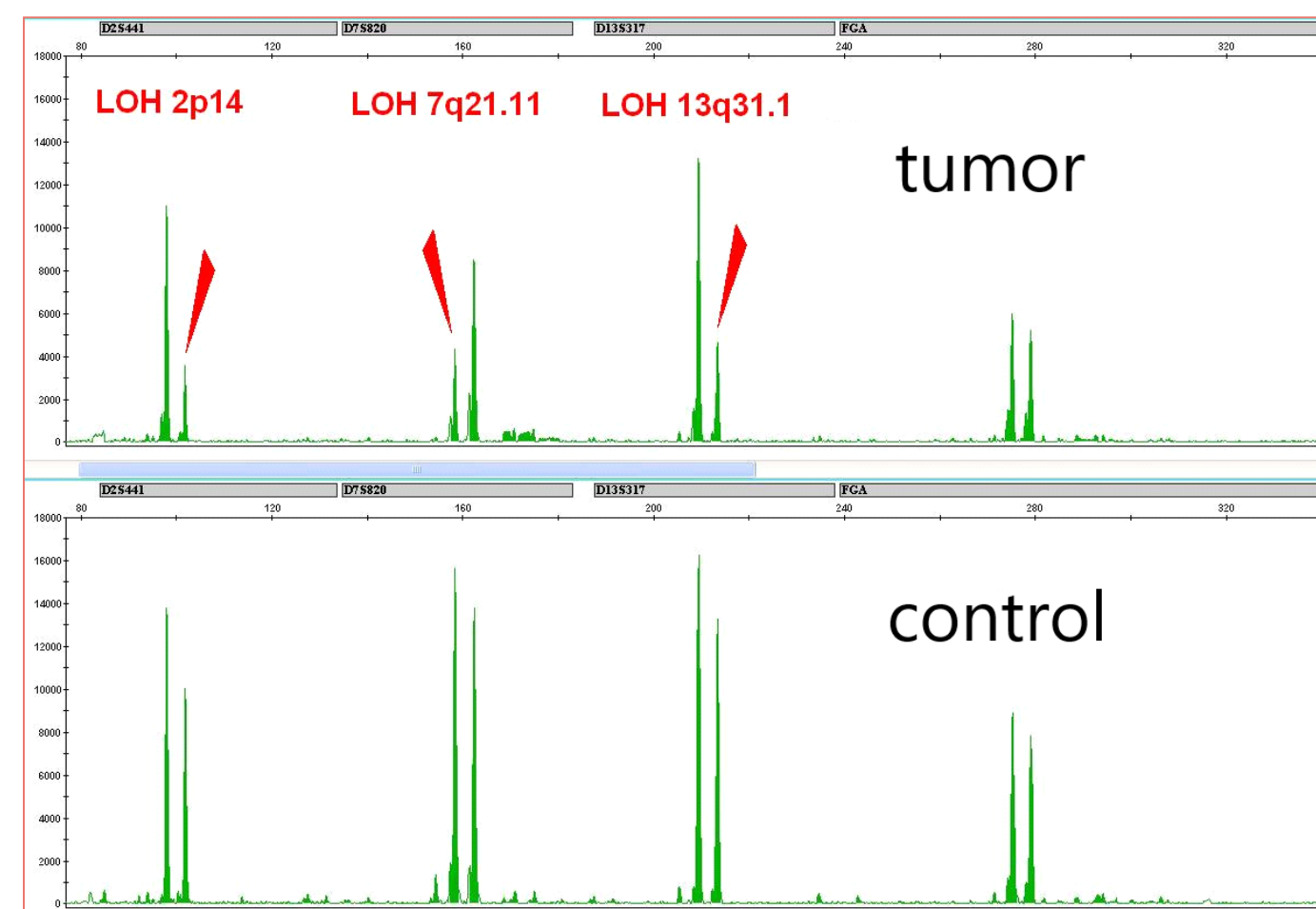
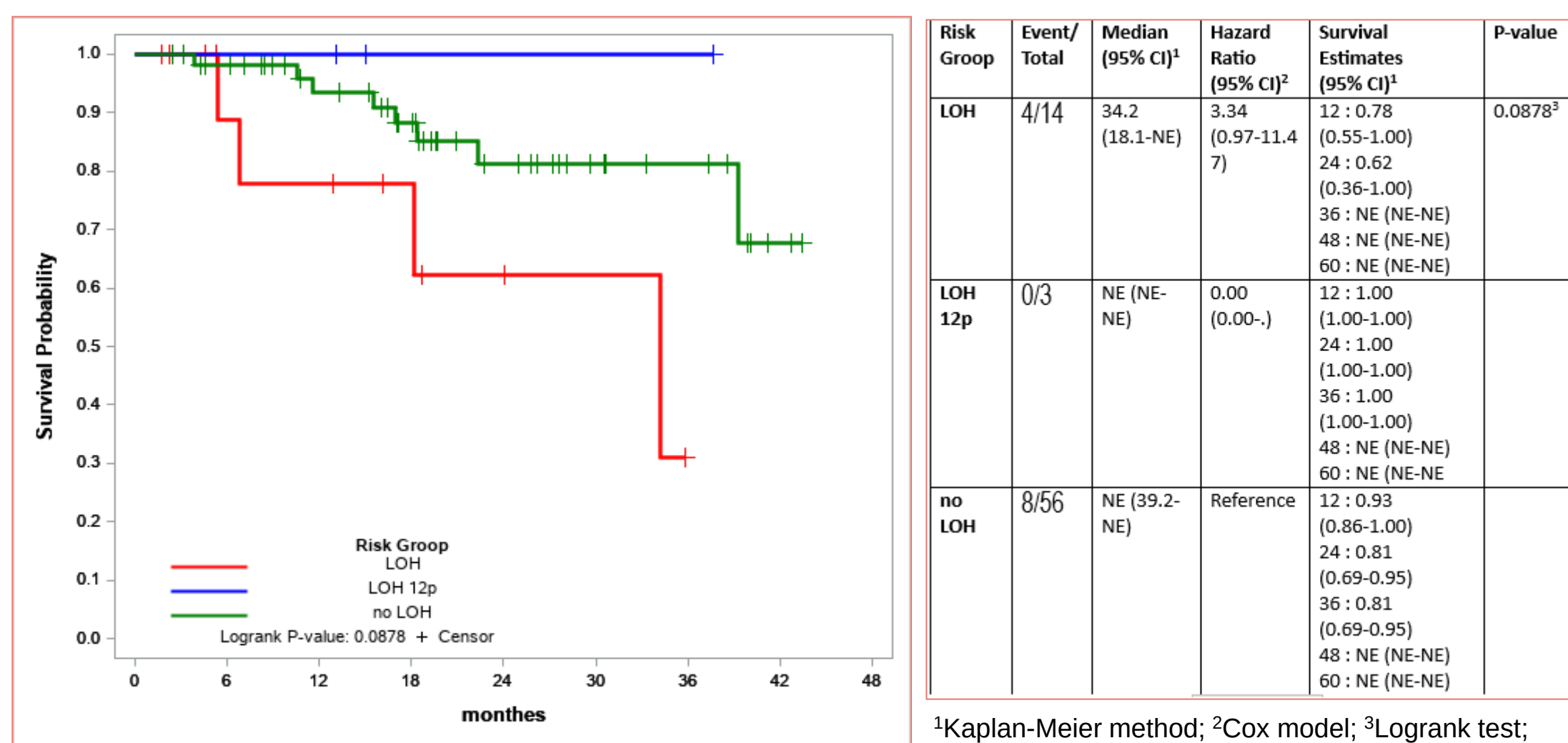


Figure 1. LOH patterns in STR profile of ALL patient

Objective

To identify LOH in the blast cells of the patients with B- and T-ALL at diagnosis and to analyze therapy outcomes according to LOH status.



¹Kaplan-Meier method; ²Cox model; ³Logrank test;

Figure 2. Kaplan-Meier survival curve for OS estimates according to the LOH status in tumor STR profile (LOH (exc. LOH 12p), LOH 12p, no LOH)

Materials & Methods

DESIGN: This study includes an analysis of the STR profiles in the DNA of tumor cells on a cohort of 87 patients with de novo -diagnosed Ph-negative ALL (40 B-ALL, 44 T-ALL, 3 biphenotypic ALL) and statistical evaluation of LOH as a possible risk factor for B- and T-ALL. All patients were treated according to the "RALL-2016" regimen at the National Research Center for Hematology (Moscow, Russia)

SETTING: 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 CoDIS Plus multiplex kit (Gordiz Ltd, Russia). LOH in tumor DNA was verified by chromosomal microarray (CMA CytoScanHD).

PATIENTS: Inclusion criteria: de novo-diagnosed Ph-negative ALL patients, 18–55 years old, an intermediate-risk group without MLL translocation t(4;11)(q21;q23), and treatment by RALL-2016 protocol. Exclusion criteria: patients older than 55 years, MLL translocation t(4;11)(q21;q23), and pretreatment.

MAIN OUTCOMES MEASURES: A 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.

Results

Of the 87 patients, 21 were found with LOH in certain STR loci (24%). 12p LOH was detected in 8 patients. According to OS analysis, LOH 12p seems to be a marker of a favorable prognosis (Fig.2). Patients with the 12p LOH are excluded from the risk group because 12p LOH is not associated with worse outcome according to our data and to some publications [4]. For B-ALL patients LOH (excepting 12p LOH) was an independent risk factor (OS hazard ratio 3.89, log-rank P-value 0.0395) (Fig.3a). For T-ALL patients OS hazard ratio was 0.59 (log-rank P-value 0.62)(Fig.3b).

Conclusions

LOH in some STR loci established for de novo diagnosed ALL could be used as a prognostic factor for possible poor clinical outcome. We have found a statistically significant association of clinical failures with the LOH in STR loci measured at the onset of B-ALL, but not of T-ALL.

Funding

This study was supported by Rakfond grant 5/2019

References

- Malard F, Mohty M. Acute lymphoblastic leukaemia. *Lancet*. 2020
- Bassan R, Pavoni C, Interimesoli T et al Updated risk-oriented strategy for acute lymphoblastic leukemia in adult patients 18-65 years: NILG ALL 10/07. *Blood Cancer J*. 2020
- Peterson JF, Van Dyke DL, Hoppman NL et al The Utilization of Chromosomal Microarray Technologies for Hematologic Neoplasms: An ACLPS Critical Review. *Am J Clin Pathol*. 2018
- Takeuchi, S., Seriu, T., van Dongen, J. et al. Allelotype analysis in relapsed childhood acute lymphoblastic leukemia. *Oncogene* 2003