Frequency and clinical relevance of DNA microsatellite alterations of the *CDKN2A/B*, *ATM* and *p53* gene loci: a comparison between pediatric precursor T-cell lymphoblastic lymphoma and T-cell lymphoblastic leukemia

David Krieger,[1] Anja Moericke,[2] Ilske Oschlies,[3] Martin Zimmermann,[1] Martin Schrappe,[2] Alfred Reiter,[1] and Birgit Burkhardt[1,2]

[1]Department of Pediatric Hematology and Oncology, Justus Liebig University, Giessen; [2]Department of Pediatrics, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, and [3]Department of Pathology, Hematopathology Section and Lymph Node Registry, University Hospital of Schleswig-Holstein, Campus Kiel, Germany

ABSTRACT

Although deletions of cell cycle regulatory gene loci have long been reported in various malignancies, little is known regarding their relevance in pediatric T-cell lymphoblastic lymphoma (T-LBL) and T-cell lymphoblastic leukemia (T-ALL). The current study focused on loss of heterozygosity (LOH) analyses of the *CDKN2A/B* (chromosome 9p), *ATM* (chromosome 11q) and *p53* (chromosome 17p) gene loci. Frequencies of LOH were compared in 113 pediatric T-LBL and 125 T-ALL who were treated uniformly according to ALL-BFM strategies. Furthermore, LOH findings were correlated with clinical characteristics and tested for their prognostic relevance. LOH at 9p was detected in 47% of T-LBL and 51% of T-ALL, and was associated with male gender in both. In T-ALL, LOH at 9p was associated with favorable initial treatment response. A tendency for favorable event-free-survival was observed in LOH 9p positive T-LBL. The frequency of LOH at chromosomes 11q and 17p was 5% or less for both diseases.

Key words: lymphoblastic lymphoma, lymphoblastic leukemia, *LOH*, *CDKN2A/B*, *ATM*, *p53*.

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Introduction

Pediatric lymphoblastic precursor T-cell neoplasms are currently classified as either acute lymphoblastic T-cell leukemia (T-ALL) or lymphoblastic T-cell lymphoma (T-LBL) depending on bone marrow (BM) involvement: in case of 25% or over BM involvement a diagnosis of T-ALL is made, in case of less than 25% BM involvement T-LBL is diagnosed. Both are often considered as different manifestations of one and the same disease because of biological and clinical similarities. Nevertheless, T-LBL and T-ALL might harbor different biological potentials due to certain differences of immunophenotypic and molecular genetic parameters which were reported recently.[1-3] Beside other molecular mechanisms, chromosomal deletions with consecutive loss of tumor suppressor genes have been reported as contributors to the pathogenesis of ALL.[4,5] The most common deletions in T-ALL are located at chromosome 9p21, which contains the *CDKN2A/B* gene encoding for cyclin-dependent kinase inhibitors $p16^{INK4A}$, $p15^{INK4B}$ and the alternative reading frame protein of the *CDKN2A* locus $p14^{ARF}$. These proteins negatively regulate G1 to S transition of cell cycle and thus prevent cell division. The tumor suppressor gene *p53* on chromosome 17p represents another key regulator of apoptosis and cell cycle arrest upon DNA damage, which is frequently altered in solid tumors. However, in pediatric T-LBL and T-ALL, alterations of *p53* are reported to be rare events.[6,7] The ataxia teleangiectasia mutated gene (*ATM*), located on chromosome 11q22, is a tumor suppressor gene acting upstream of p53. *ATM* is activated by DNA damage and phosphorylates proteins, such as p53. The *ATM* gene is reported to be frequently deleted in lymphoid malignancies, including childhood ALL.[8-10] Data on *ATM* alterations in T-LBL are still lacking. On the whole, deletions and loss of heterozygosity of several key regulator genes of the G1 to S transition of cell cycle have been reported for lymphoid malignancies. However, the frequency of these alterations and their prognostic relevance still remains to be clarified for pediatric T-cell lymphoblastic lymphoma and leukemia. The current study focused on LOH analyses of the *CDKN2A/B* locus, the *ATM* locus and the *p53* locus, comparing the results obtained in 113 pediatric T-LBL cases with the findings obtained in 125 pediatric T-ALL samples.

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Correspondence: Birgit Burkhardt, Department of Pediatrics, University Hospital Schleswig-Holstein, Campus Kiel, Arnold-Heller Str. 3 Haus 9, 24105 Kiel, Germany. E-mail: birgit.burkhardt@uk-sh.de
The online version of this article has a supplementary appendix.

Design and Methods

Patients

Between April 1995 and June 2007 264 T-LBL-patients were registered in the NHL-BFM study center (Non-Hodgkin's Lymphoma Berlin-Frankfurt-Munster Group) after informed consent. Of these, 113 T-LBL patients with available tumor and germ-line DNA were evaluable for LOH-analysis.

Between August 1999 and July 2002, 186 pediatric T-ALL patients were registered in the ALL-BFM study center after informed consent, from which 125 were evaluable for LOH analysis. In both T-LBL and T-ALL, there was no difference in clinical characteristics between evaluable and non-evaluable patients (*Online Supplementary Tables S1 and S2*). The studies were approved by the ethics committees responsible.

Diagnosis and therapy

T-LBL were classified according to WHO-Classification of Haematological Malignancies, and were treated according to an ALL-BFM-type treatment strategy.[11]

T-ALL, diagnosed by cytomorphology and flow cytometry analyses of bone marrow (BM) and peripheral blood (PB) were also treated according to ALL-BFM treatment strategy.[12]

DNA microsatellite analysis

The following set of microsatellite markers were analyzed: D9S1869, D9S285, D9S157, D9S162, D9S171 flanking the gene locus *CDKN2A/B* (chromosome 9p), D11S1339, D11S2179, D11S1294, D11S4206, D11S4090 flanking the *ATM* gene locus (chromosome 11q), and the common marker TP53 for the *p53* gene (chromosome 17p). Primer sequences, were retrieved from Genome Database (*GDB http://www.ncbi.nlm.nih.gov*) and Ensembl database (*www.ensembl.org*) (*Online Supplementary Table S3*). The PCR primers were synthesized by MWG Biotech (Ebersberg, Germany). Preparation of DNA and microsatellite analysis was performed as described previously.[3,13]

Statistical analysis

The probability of event-free survival (pEFS) was calculated according to Kaplan and Meier with differences compared by the log-rank test. pEFS was calculated from the date of diagnosis to the first event (death from any cause, relapse, resistant disease, or second malignancy) or to the date of the last follow-up. Patients lost to follow-up were censored at the time of their last follow-up examination. Differences in the distribution of individual parameters among patient subsets were analyzed using the χ^2 test or Fisher's exact test. Statistical analyses were conducted using the SAS statistical program (SAS-PC, Version 9.1, Cary, NC: SAS Institute Inc.). Follow-up data were updated in June 2008.

Results

Precursor T-cell lymphoblastic lymphoma

In T-LBL, DNA microsatellite marker analyses of germline DNA and tumor DNA were successful for a total of 1,132 markers. LOH was found in 181 (16%), retention of the heterozygous status in 637 (56%), homozygous pattern in 299 (26%) and microsatellite instability in 15 (1%) markers.

Precursor T-cell lymphoblastic leukemia

For the 125 T-ALL patients, LOH analyses showed a total of 1,364 successfully analyzed markers. LOH was detected in 222 (16%), retention of heterozygous status in 846 (62%), homozygous pattern in 293 (21%) and microsatellite instability in 3 (less than 1%) markers, respectively.

Frequency of DNA microsatellite alterations according to targeted loci

The most frequent alteration in both T-LBL and T-ALL was LOH at chromosome 9p. The rate of LOH 9p positive patients was 47% and 51%, respectively. For T-LBL and T-ALL, LOH rates were 5% and 2% at chromosome 11q, and 4% and 1% at chromosome 17p (Table 1). The comparison of the LOH rates between T-LBL and T-ALL revealed no significant differences. The complete data of all marker results analyzed separately are shown in detail in the *Online Supplementary Table S4*.

In the 113 T-LBL patients, 3 patients showed LOH 9p and LOH 11q. One patient had LOH 9p and LOH 17p. In 48 T-LBL patients, LOH 9p was found, 2 patients had LOH 11q and another 2 patients LOH 17p, while 57 patients were LOH negative for all three loci.

For the 125 T-ALL patients, LOH 9p combined with LOH 11q was detected in 2 patients. One T-ALL patient showed LOH at 9p and 17p. Sixty-one T-ALL patients had LOH 9p, one patient had LOH 11q and 60 patients showed no findings of LOH.

Table 1. Results of the loss of heterozygosity (LOH) analyses per locus in patients with lymphoblastic T-cell lymphoma (T-LBL) and patients with acute T-cell leukemia (T-ALL).

	T-LBL patients (n=113)			T-ALL patients (n=125)			*P* value (Fisher)
	N. of informative pts	N. of LOH+ pts	Rate of LOH+ pts (CI*)	N. of informative pts	N. of LOH+ pts	Rate of LOH+ pts (CI*)	
LOH at 9p (CDKN2A/B)	110	52	47% (38-57%)	125	64	51% (42-60%)	0.60
LOH at 11q (ATM)	110	5	5% (2-10%)	125	3	2% (1-7%)	0.48
LOH at 17p (TP53)	72	3	4% (1-12%)	109	1	1% (0.2-5%)	0.62

*LOH+: positive findings of loss of heterozygosity, Rate of LOH+ pts: Rate of patients with loss of heterozygosity, *CI: 95% confidence interval.*

Association of patients' characteristics with DNA microsatellite alterations

To examine the association of DNA alterations with clinical characteristics, the following parameters were considered: gender, age, CNS involvement, mediastinal tumor, prednisone response day 8 (T-ALL), BM response day 15 (T-ALL), initial BM involvement (T-LBL) and stage of disease (T-LBL).

Table 2 displays the analyses of clinical characteristics for T-LBL and T-ALL patients according to their LOH 9p status. In T-LBL, the only statistically significant finding was the association of LOH at 9p with male gender (Table 2A). A similar male predominance was found in LOH 9p positive T-ALL patients (Table 2B). Noteworthy was a trend for an increased rate of prednisone good responders at day 8 and a statistically significant favorable bone marrow response at day 15 for LOH 9p positive T-ALL patients. LOH analyses of the *ATM* (11q) and *p53* gene loci (17p) were hampered by the low rate of LOH in both T-LBL and T-ALL. Therefore, no statistically significant association with clinical characteristics was found for these loci.

DNA microsatellite alterations and outcome

EFS of LOH 9p positive T-LBL at 5-years was 84±5% compared with 75±6% in LOH 9p negative T-LBL (*P* value log rank 0.28) (*Online Supplementary Figure S1A*). In T-ALL pEFS at 5-years was 80±5% in LOH 9p positive T-ALL versus 74±6% in LOH 9p negative T-ALL (*P* value log rank 0.53) (*Online Supplementary Figure S1B*). There was no statistically significant association between microsatellite alteration and outcome of any of the targeted loci (Table 3).

Table 2. Patients' characteristics with or without LOH at chromosome 9p for pediatric precursor T-lymphoblastic lymphoma (T-LBL) cases (A) compared with precursor T-lymphoblastic leukemia (T-ALL) cases (B). Data refer to patients with successful investigation of the respective criteria.

A

Patients' characteristics	T-LBL without LOH at 9p (N=58)		T-LBL with LOH at 9p (N=52)		*P* value (F)
Gender					
female	23	40%	9	17%	
male	35	60%	43	83%	0.01
Age (years)					
<10	36	62%	32	62%	
10–14	17	29%	17	33%	
>14	5	9%	3	6%	0.83
Stage of disease					
stage I	0	0%	0	0%	0.73
stage II	0	0%	1	2%	
stage III	43	75%	35	71%	
stage IV	14	25%	13	27%	
BM involvement	12	21%	12	23%	0.82
Mediastinal tumor	54	93%	50	96%	0.68
CNS involvement	2	4%	3	6%	0.66

B

Patients' characteristics	T-ALL without LOH at 9p (N=61)		T-ALL without LOH at 9p (N=64)		*P* value (F)
Gender					
female	21	34%	9	14%	
male	40	66%	55	86%	0.01
Age (years)					
<10	30	49%	37	58%	
10–14	20	33%	16	25%	
>14	11	18%	11	17%	0.60
Mediastinal tumor	35	59%	44	71%	0.19
CNS involvement	2	4%	6	11%	0.28
Prednisone response					
PGR	31	53%	45	70%	0.06
PPR	28	48%	19	30%	
BM response at day 15					
M 1	18	33%	32	58%	
M 2	12	22%	11	20%	
M 3	25	46%	12	22%	0.01

LOH: Loss of heterozygosity, F: P value calculated according to Fisher's exact test, BM: bone marrow; PGR: prednisone good response at day 8, PPR: prednisone poor response at day 8.

Table 3. Univariate analysis of 5-year event free survival for pediatric precursor T-lymphoblastic lymphoma (T-LBL) cases and precursor T-lymphoblastic leukemia (T-ALL) cases according to LOH status. Data refer to patients with successful investigation of the respective criteria.

	T-LBL					T-ALL				
	LOH-		LOH+			LOH-		LOH+		
	N. pts	pEFS	N. pts	pEFS	*P* value (LR)	No pts	pEFS	No pts	pEFS	*P* value (LR)
LOH at 9p (*CDKN2A/B*)	58	75±6%	52	84±5%	0.28	61	74±6%	64	80±5%	0.53
LOH at 11q (*ATM*)	105	79±4%	5[1]	100%[1]	0.30	122	78±4%	3[1]	33±27%[1]	
LOH at 17p (*p53*)	69	76±5%	3[1]	100%[1]	0.36	108	77±4%	1[1]	100%[1]	

LOH-: no findings of loss of heterozygosity, LOH+ positive findings of loss of heterozygosity, LR: log rank test, pEFS: probability of event-free survival at 5-years, [1]due to the small number of LOH+ patients the data must be discussed with caution. The numbers are too small to draw any conclusion on the prognostic significance.

Microsatellite instability

Beside LOH, microsatellite instability (MSI) was detected. MSI is a change in the number of microsatellite repeats, due to abnormal DNA repair mechanisms, resulting in altered fragment lengths. MSI was detected only sporadically and did not allow for statistical analysis (*data not shown*).

Results and Discussion

To our knowledge the current report represents by far the largest series of T-cell lymphoblastic lymphoma (T-LBL) and leukemia (T-ALL) patients evaluable for DNA microsatellite analyses of three DNA loci encoding for critical cell cycle regulatory molecules: *CDKN2A/B*, *ATM* and *p53*. T-LBL and T-ALL patients were treated uniformly according to ALL-BFM strategies, allowing the analysis and comparison of the impact of DNA alterations on prognostic parameters and outcome.

Loss of heterozygosity (LOH) analysis of these loci was performed as an indirect technique for the search of chromosomal deletions. Advantages of this method are the minimal requirements on amount and quality of samples, which is of particular importance for the systematic analyses of diseases with scarcity of tumor material, e.g. pediatric lymphoblastic lymphoma.

In pediatric T-ALL, deletions of *CDKN2A/B* examined with molecular genetic methods have been reported in about 30-70% of the cases, with higher frequency in T-ALL compared to pB-ALL.[14-17] Yet, the prognostic significance of *CDKN2A/B* deletions remains inconclusive. Depending on the study design and the composition of the analyzed population, *CDKN2A/B* deletions were either of no prognostic value[14,15] or associated with poor prognostic parameters and inferior outcome.[17-21] However, most studies on childhood ALL included precursor B- and T-cell leukemia, with T-ALL representing less than 20% of the entire population. Focusing on T-cell immunophenotype, the current study revealed LOH in 51% of T-ALL patients. Interestingly, LOH at 9p was associated with male gender, which had not been described in earlier reports. Furthermore an association of LOH at 9p with favorable initial treatment response in T-ALL at day 8 and day 15 could be shown. This association with good response to initial treatment did not translate into a statistically significant superior pEFS, but pEFS was slightly favorable for LOH 9p positive T-ALL patients. The current findings of an association with male gender, good initial response and at least equal pEFS in LOH 9p positive T-ALL might be attributed to the project's research focus on a biologically well defined and uniformly treated group of patients. The necessity of differentiation according to immunophenotype had already been reported earlier by Heerema *et al.*, who showed significant inferior pEFS for pediatric ALL with cytogenetic abnormalities at chromosome 9p; however, this difference in pEFS lost its statistical significance when analyzed for T-ALL patients separately.[22]

Until today, data on the frequency of *CDKN2A/B* deletions in T-LBL are rare, while those of prognostic value are still lacking. The current report shows data on T-LBL, detecting a LOH 9p rate of 47%, which is similar to 51% in T-ALL. Just as in T-ALL, LOH at 9p was associated with male gender in T-LBL. Interestingly, pEFS for LOH 9p positive T-LBL patients was 84±5% versus 75±6% for LOH 9p negative T-LBL patients (*P* value 0.28). This might be an indicator that LOH 9p could be associated with good response to treatment and favorable outcome in T-LBL. Unfortunately, valid criteria for response evaluation are lacking in T-LBL, so that it was not possible to compare the finding of good initial response in LOH 9p positive T-ALL with similar benchmarks in T-LBL. For the *ATM* gene locus and *p53* the LOH rates were 5% or less in both diseases which hampered further analysis on association with clinical characteristics or prognosis.

Little is known on the comparison of molecular profiles of pediatric T-LBL and T-ALL. Recent reports noted both similarities and differences.[1-3] The current study, therefore, focused on DNA microsatellite alterations in genomic loci encoding for key molecules of cell cycle regulation comparing frequency, association with clinical characteristics and prognostic relevance within uniformly treated populations. Owing to the robust method of LOH analyses, it was possible to investigate such large populations. The current study revealed comparable figures in T-LBL and T-ALL, suggesting the two diseases might share common mechanisms of cell cycle deregulation resulting in uncontrolled proliferation of the precursor T-cell lymphoblasts.

Authorship and Disclosures

BB designed research and takes primary responsibility for the paper. DK and BB performed laboratory work. BB, DK and AR co-ordinated the research. MZ provided statistical

analysis. IO performed central histopathological review and provided samples. AR and BB provided samples and clinical data of T-LBL cases. MS and AM provided samples and clinical data of T-ALL cases. All authors contributed to the interpretation of results. BB, DK and AR wrote the paper.

The authors reported no potential conflict of interest.

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