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Evaluation of *BAALC*- and *WT1*-expressing leukemic cell precursors in pediatric and adult patients with *EVI1*-positive AML by means of quantitative real-time polymerase chain reaction (RT-qPCR)

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Summary

Some basic biological and cytogenetic characteristics of leukemic cells in *EVI1*-positive (*EVI1*$^+$) acute myeloid leukemia (AML) are shown to be different for pediatric and adult patients, like as their response to chemotherapy and hematopoietic stem cell transplantation (HSCT). Hence, one may also expect different pathogenetic roles of leukemic precursors in these AML variants. Our aim was to check this opportunity, and we have quantitatively assessed mRNA expression by leukemic precursors using a recently proposed *BAALC/WT1* molecular panel. The levels of *BAALC*, *WT1* and *EVI1* gene expression were determined simultaneously in bone marrow samples from 8 pediatric and 6 adult patients with *EVI1*$^+$ AML by means of quantitative real-time polymerase reaction (RT-qPCR) at specified time-points: a) upon primary diagnosis, b) prior to HSCT, and c) during post-transplant relapse (PTR). Blast cell counts were also provided for these bone marrow samples. Our study showed *BAALC* gene overexpression in both groups at all the tested stages. Before hematopoietic stem cell transplantation (HSCT) *BAALC* overexpression was revealed in 6 of 14 patients which could be associated with real difficulties for chemotherapy preparation for HSCT in this category of patients. Moreover, *BAALC*, or combined *BAALC/WT1* overexpression were revealed in most patients with posttransplant relapse (PTR), thus suggesting a crucial role of *BAALC*-expressing precursors for the emerging relapses. Worth of note, *BAALC* overexpression was absent at all the tested stages of M3 and M7 FAB-variants, probably, due to more mature nature of appropriate precursor cells. In general, determination of *BAALC*- and *WT1*-expressing precursors by means of RT-qPCR seems to be a promising approach to the studies of precise pathogenetic mechanisms in different AML variants, as well as to diagnostics of emerging relapses and, thus, it may be quite important for clinical practice.

Keywords

Acute myeloid leukemia, *EVI1*-positive, pediatric, adults, hematopoietic stem cell transplantation, relapses, *BAALC* expression, *WT1* expression, *EVI1* expression, leukemic cell precursors, quantitative PCR.

Introduction

Previous studies have shown heterogeneity of leukemia-producing cell populations in the patients with acute myeloid leukemia (AML) [1]. In model experiments with human leukemic cells transplanted into immunodeficient mice, the earlier CD34+CD38- human stem cells were responsible for leukemia induction and, moreover, were able to express a pan-specific Brain And Acute Leukemia Cytoplasmic (*BAALC*) gene [2, 3]. Moreover, similar experiments with acute promyelocytic leukemia (APL) cells revealed more mature leukemia-initiating precursors [4 Patel et al, 2012], which, along with blast cells, according to our hypothesis, might express *WT1*, another pan-specific gene [5-7]. Since mRNA of the both genes may be detected with quantitative real-time PCR (RT-qPCR), we attempted to evaluate the genes of interest by means of this standard approach [5-7]. Our works have yielded the following results: a) important role of *BAALC* expressing stem-cells in post-transplant relapses (PTR) of AML [5-6]; b) proven clinical effect of a targeted drug (Mylotarg) upon the levels of leukemic stem cells and precursors [7]; and c) possible presence of leukemic hematopoietic regulators causing transition from some immature stem cells in AML to more mature precursors [5, 7] as well as in APL [6]. To support this hypothesis, we have recently studied leukemic hematopoiesis in a mixed group of adult and pediatric patients with *EVI1*-positive AML. Chromosome aberrations at the 3q26 locus are considered common in adult patients, however, being virtually absent in pediatric cases. Meanwhile, *EVI1*-positive AML with presumable rearrangements of KMT2A gene was found in one-fourth of pediatric patients [8-10], thus also presenting essential age-dependent differences in responses to therapy and HSCT. At the same time, an excellent response to retinoid treatment has been recently revealed in all types of *EVI1*-positive AML [11], which seems to be associated with their direct action upon functional activity of stem cells [12].

The aim of our work was to test *BAALC/WT1* molecular panel in the mixed pediatric and adult cohort of patients with of AML variants which are generally resistant to intensive therapy and HSCT.

Patients and methods

1.1. Patient cohort

Our retrospective study presents the data on *BAALC* and *WT1* gene expression levels measured in parallel in the course of serial bone marrow sampling from fourteen *EVI1*-positive patients with different AML FAB-variants, who underwent allogeneic HSCT at R. Gorbacheva Memorial Research Institute of Children Oncology, Hematology and Transplantation (St. Petersburg) from 2010 to 2016 years. This group included 8 pediatric patients under 18 years and 6 adults with AML. In all the patients, *BAALC* and *WT1* gene expression changes, as well as blast cell counts were serially monitored in the same bone marrow aspirates. Written informed consent was obtained from all patients, following the Declaration of Helsinki Recommendations.

1.2. Analysis of *BAALC* and *WT1* gene expression levels

Total mRNA was extracted from fresh bone marrow samples, its reverse transcription and estimation of the *BAALC* gene expression level were performed by quantitative real-time PCR (RT-qPCR) as elsewhere described [13]. In brief, *BAALC* transcript copy numbers (CN) were determined by means of *BAALC* RQ-Kit (Inogene, Russia), including plasmid standards for plotting appropriate calibration curves for *BAALC* and *ABL1* reference gene. Basic control time points for the bone marrow examination were as follows: at diagnosis (e.g., D-80), prior to conditioning (D0), and, as obligatory diagnostics, in post-transplant relapses (PTR). A median follow-up time after HSCT was 7 months (range, 0.6 to 52.5 months). Relative *BAALC* expression level was calculated as a ratio of CN_{BAALC} to CN_{ABL1} and expressed as a percent value. The expression level of 31% was chosen as a common cut-off value to study clinical significance of *BAALC* gene overexpression before and after HSCT. This value was shown to exceed maximal *BAALC* expression levels in the patients with pre-transplant cytological remission without any signs of the disease progression.

In parallel, the *WT1* gene expression levels were determined in each sample at the same time points. The copy numbers of *WT1* transcripts were evaluated by the similar RT-qPCR method, according to Recommendations of European LeukemiaNet Group [14]. The basal *WT1* expression level of 250 copies *per* 10^4 copies of *ABL1* reference gene was used to discriminate between low and high *WT1* expression rates. Similarly, the 10 per cent expression level was considered a cut-off value when studying clinical significance of *EVI1* overexpression.

1.3. Statistical analysis

Due to small numbers of patients in the tested groups, full-scale statistical analysis was not carried out. The data with asymmetric distribution were presented as extreme ranges and median values. Overall survival (OS) and relapse free-survival (RFS) were measured from D0 until the date of death, regardless of cause, or until the term of documented relapse, or last contact date. STATISTICA software was used for calculations. $P< 0.05$ was considered the statistically significant difference level, having been determined in every case.

Results

Basic clinical and laboratory data are presented in Table 1. They concern eight pediatric (lower 18 y. o.) and six adult patients. The common levels of *EVI1* expression ranged from 0.3% to 130%, being the highest in 26 year-old female with M1 FAB-variant (#11) with complex karyotype. One should note that the cytogenetic changes in pediatric patients were not related to specific 3q26 locus, whereas this pattern of chromosome aberrations was found in 5 of 6 adult patients (83%). At the same time, one of pediatric patients (#5) showed KMT2A rearrangements which are more typical to this type of childhood AML. In general, the cytogenetic aberrations ranged from chromothripsis (#1) and highly

Table 1. Clinical and laboratory parameters of pediatric (#1-8) and adult (#9-14) variants of *EVI1*-positive acute myeloid leukemia, treated with hematopoietic stem cell transplantation

#	FAB	Gender	Age	Cytogenetics	Initial phase				Before HSCT				PTR				HSCT type	Relapse (n3)	OS, days
					BAALC, %	*WT1*, copies	*EVI1*, %	*Blasts*, %	*BAALC*, %	*WT1*, copies	*EVI1*, %	*Blasts*, %	*BAALC*, %	*WT1*, copies	*EVI1*, %	*Blasts*, %			
1	7	F	1	46,XX;t (3;8), misbalanced trans-locations t(5;7), t(7;17), t(11;15), t(5,17), del(15q), r(17), der (21) with duplication some segments of 21q and ins(15q) along all longevity of derivative chromosome #21	n/d	n/d	n/d	n/d	32	46	3	16.2	9	3315	99	60.4	rel	1	98*
2	0	F	2	47, XX, r(7)(p1?q36), +21[19]/46XX[1]	n/d	16029	11	37.6	21	9	2	5-2	-	-	-	-	n/rel	0	1830
3	7	F	3	46,XX	n/d	n/d	n/d	n/d	2.5	3693	90	13.4	0.3	1049	53	20.8	n/rel	1	258*
4	?	F	3	45,XX,t(6;12)(q26;q23),-7[10]	n/d	n/d	n/d	n/d	19	234	1	8.6	100	436	22	29.8	haplo	1	355*
5	4	M	6	46XY, t(9;11)(p22;q23), del(3)(p26:q28)	n/d	1222	81	n/d	5	219	4	1.4	-	-	-	-	n/rel	0	2131
6	bi	M	8	46,XY,del(11)(q13q23)[6]/46,XY[13]/46,XX[1]	n/d	n/d	n/d	n/d	51	2048	37	7.2	121	10239	22	30.4	haplo	1	317*
7	5	M	11	45,XY,-7[14]/45,idem, del(12)(p11)[4]/46,XY[2]	45	11753	0,03	88	135	32	17.7	4.8	-	-	-	-	haplo	0	2581
8	3	F	17	46,XX,t(15;17) PML-RARα	n/d	n/d	n/d	n/d	0.8	2957	21	1.8	2.7	**32684**	321	**24.4**	n/rel	1	136*
9	4	F	21	45,XX,inv(3)(q21q26),t(2;3)(q?12;q21), -7[6]/4[14]	**107**	867	49	17	44	2025	38	9	389	1165	22	31.5	n/rel	1	83*
10	4	M	24	46,XY,inv(3)(q21q26)[13]/46,XY[7]	n/d	n/d	n/d	n/d	64	199	53	38.4	-	-	-	-	n/rel	0	628
11	1	F	26	46,-X,der(X) t(X;17)(p22; q2?5),der(1)t(1;17)(p36;q2?1),inv(11)(p15q22),+21[3]/46,-X,der(X)t(X;17)(p22;q2?5),der(1)t(1;3)(p36;q26),inv(11)(p15q22),+21[2]/46,XY[15]	130	10493	23	84,2	10	61	1	3.4	125	6500	22	51.2	n/rel	1	400*
12	5	M	37	46,XY,t(3;12)(q26;p13)[11] /45,XY-,idem,-7[2]/46,XY, idem,+mar[7]	n/d	n/d	n/d	n/d	2	77	54	3.8	24	4542	88	21	rel	1	195*
13	2	M	39	48,XY,+9,del(11)(p13),+21[2]/46,XX[28],	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	83	18872	10	26	n/rel	1	77*
14	2	M	56	45,XY,inv(3)(q21q26),-7[15]	n/d	n/d	n/d	n/d	58	2671	26	7.6	n/d	n/d	n/d	n/d	rel	2	124*

*, deceased patients; n/d, no data; rel, related; n/rel, nonrelated; haplo, haploidentical; overexpressed levels of *BAALC* expression and higher meanings of OV in children are noted by red and green colours, respectively

complex karyotype to single reciprocal translocations (#8) or deletions (#6). Normal karyotype was registered only in one child (#3).

One should comment that primary diagnosis in most patients was assessed at regional hospitals, where precise molecular diagnostics was not available. Therefore, molecular markers at the early stages of disease are lacking in these patients.

Despite this drawback, elevated *BAALC* expression in *EVI1*-positive AML at primary diagnosis was demonstrated both in pediatric (#7) and adult (#9, 11) patients, being higher in adults.

Before HSCT, overexpression of *BAALC* was seen in three pediatric patients (#1, 6, 7), as well as in two adults (#9, 14) who, along with increased blast counts, showed insufficient response of these leukemic cells to pretransplant therapy. This pattern of response is also confirmed by common elevation of *WT1* level expression prior to HSCT (6/13; 46%). Finally, upon emergence of post-transplant relapse (PTR) in 5/6 adult patients and 5/8 pediatric ones, the elevated *BAALC* expression was revealed in five cases (#4, 6, 9, 11 and 13), being the highest (389%) in a young female with secondary (from MDS) M4-FAB-variant of AML (# 9). *WT1* gene expression at diagnosis, was enhanced in patients #7, #9 and #11 (11753, 867 and 10493 copies, respectively), with appropriate increase of blast numbers in bone marrow (resp., 88%, 17%, and 84%). At pre-transplant stage, the levels of *WT1* expression were increased in the patients #3, #6, #8, #9 and #14 (up to 3693, 2048. 2957. 2025 and 2671 copies, respectively), showing only weak correlation with blast counts in their bone marrow samples (13.4, 7.2, 21, 38 and 7.6, respectively.) Comparison of these data argues for our earlier concept presuming an active participation of other cell populations in *WT1* gene expression, for instance, of more mature precursors recently found in successful xenograft of APL samples in immunodeficient NOD/shi-SCID IL2Ry-/- mice [4].

Finally, at stage of PTR, increased *WT1* expression levels were found in patients #1, 3, 4, 6, 8, 9, 11, 12, and 13 (respectively, 3315, 1049, 436. 120239. 32684, 1165, 6500, 4542 and 18872 copies) that also weakly correlated with number of blasts in tested bone marrows (60.4, 20.8, 29.8, 30.4, 24.4, 31.5, 51.2, 21, and 26%, respectively).

In conclusion, one should notice that the patients with M3 (#8) and M7 (#1 and 3) had lower levels of *BAALC* expression at all studied stages, which is explained simply by basic role in hematopoiesis with more mature precursors than *BAALC*-expressing stem cells. Further, one may conclude on opportunity for different variants of emerging PTR. Thus, in several cases (#4, 6, 9, 11, and 13), PTR were associated with activation of both *BAALC*-expressing stem cells and *WT1*-expressing mature precrsors. Meanwhile, PTR in patients with M3 (#8), M7 (# 1 , 3 and single presenters of M5 (#12) FAB-variants were accompanied by *WT1* expressing precursors only.

Discussion

Hence, despite different biological and cytogenetic characteristics of pediatric and adult *EVI1*-positive AML, they revealed relatively higher levels of *BAALC*-expressing precursors at diagnosis, as well as at pre- and posttransplant stages, which, in turn, may be related with great difficulties in preparative regimens for HSCT. The real difference between the age groups consisted only in more often relapse-free course of leukemia in children (n=3), than that was among adults (n=1). Therefore, median of overall survival in pediatric patients was longer than that in adults (999 *vs* 317 days, respectively) which is statistically significant ($p<0.05$). Presence of cases with AML FAB-variants of M7 (n=2) and M3 (n=1) in pediatric group among these patients may be another reason for absence of expected difference in OS. These patients, generally, do not show higher levels of *BAALC* expression, due to alternative nature of hematopoiesis precursors.

Conclusion

To reveal the expected difference in *BAALC*-expressing precursors between pediatric and adult *EVI1*-positive AML, further studies should be performed in larger cohorts of carefully chosen patients, with omission of M7 and M3 FAB-variants.

Our simultaneous measurements of *BAALC* and *WT1*-expressiong leukemic precursors by means of standardized RT-qPCR supported crucial role of *BAALC*-expressing stem cells in pathogenesis of *EVI1*-positive AML and relapses evolving in both tested groups.

Conflict of interest

None reported.

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Оценка *BAALC*- и *WT1*-экспрессирующих лейкозных клеток-предшественников у детей и взрослых с *EVI1*-позитивным острым миелобластным лейкозом посредством количественной ПЦР в режиме реального времени

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Резюме

Показано, что ряд основных биологических и цитогенетических характеристик лейкозных клеток при *EVI1*-позитивном (*EVI1*$^{+}$) остром миелобластном лейкозе (ОМЛ) различен у пациентов детского возраста и взрослых, как и их ответ на химиотерапию и трансплантацию гемопоэтических стволовых клеток (ТГСК). Таким образом, можно ожидать и различную патогенетическую роль лейкозных клеток-предшественников при данных вариантах ОМЛ. Нашей целью была проверка этой возможности, и мы количественно определяли экспрессию мРНК лейкозными клетками-предшественниками с применением недавно предложенной молекулярной модели оценки *BAALC/WT1*. Уровни экспрессии генов *BAALC*, *WT1* и *EVI1* определяли параллельно в образцах костного мозга у 8 пациентов детского возраста и 6 взрослых с *EVI1*$^{+}$ ОМЛ с помощью количественной ПЦР в реальном режиме времени (РТ-кПЦР) в конкретные сроки: а) при первичной диагностике, б) перед ТГСК и в) на фоне посттрансплантационного рецидива (ПТР). Подсчет бластных форм проводили в этих же образцах костного мозга. Наши результаты показали наличие гиперэкспрессии гена *BAALC* в обеих группах на всех этапах исследования. Гиперэкспрессия *BAALC* перед проведением ТГСК выявлялась у 6 из 14 пациентов, что может быть связано с реальными сложностями химиотерапии для последующей ТГСК в этой категории больных. Кроме того, поскольку гиперэкспрессия *BAALC* или *BAALC/WT1* была обнаружена у большинства пациентов с рецидивом после ТГСК, можно предполагать о ключевой роли *BAALC*-экспрессирующих предшественников в развитии рецидива.

Надо отметить, что гиперэкспрессия *BAALC* не выявлялась во всех исследованных этапах при М3- и М7-вариантах ОМЛ, возможно, благодаря большему уровню дифференцировки соответствующих клеток-предшественников. В целом, определение *BAALC*- и *WT1*-экспрессирующих предшественников посредством РТ-кПЦР представляется перспективным подходом к исследованиям конкретных патогенетических механизмов при различных вариантах ОМЛ, а также при диагностике возникающих рецидивов и может быть весьма важным для клинической практики.

Ключевые слова

Острый миелобластный лейкоз, *EVI1*-позитивный, дети, взрослые, трансплантация гемопоэтических стволовых клеток, рецидивы, экспрессия *BAALC*, экспрессия *WT1*, экспрессия *EVI1*, предшественники лейкозных клеток, количественная ПЦР.