Prognostic significance of BAALC overexpression in patients with AML during the posttransplant period

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Summary

Acute myeloid leukemia (AML) is a heterogenous clonal blood disease of a neoplastic origin. There are challenging issues for the intermediate-risk AML group, which is defined as non-homogeneous due to a variety of gene mutations (FLT3, NPM1, CEBPA, etc.), prediction of differential clinical course, relapse risk, and selection of adequate therapy. In this context, a search for new molecular markers with sufficient prognostic value for the relapse risk estimation in AML cases with no detectable cytogenetic abnormalities represents a high-priority task for clinical molecular oncohematology. We analyzed prognostic significance of BAALC (Brain And Acute Leukemia, Cytoplasmic) gene overexpression in 93 AML patients during the posttransplant period, in order to estimate feasibility of BAALC expression level monitoring, to predict the relapse risk, and to evaluate sensitivity and specificity of BAALC gene expression assay, to the purpose of minimal residual disease (MRD) monitoring. BAALC expression was determined by quantitative real-time polymerase chain reaction in fresh bone marrow samples. Patients were dichotomized at BAALC’s individual and general cut-off into low and high expressers. We have concluded that BAALC overexpression above both individual and common cut-off levels is recognized as a prognostically significant factor for posttransplant relapse risk estimation, overall survival and relapse-free survival. A more detailed analysis of BAALC as a marker for estimation of therapeutic efficiency was performed. We have also compared its sensitivity to the reference techniques for minimal residual disease monitoring (i.e., qPCR-based detection of chimeric gene transcripts), showing inferior sensitivity of such approach to MRD detection in post-transplant period, at least, for our study group. Serial BAALC monitoring may be recommended for clinical relapse prediction during the post-transplant period in AML patients.

Keywords

Acute myeloblastic leukemia, BAALC, gene expression, clinical prognosis, minimal residual disease.
Introduction

Acute myeloid leukemia (AML) is a clinically heterogeneous clonal blood malignancy. Stratification of the patients into certain AML risk group is primarily based on the presence or absence of cytogenetic aberrations specific to certain leukemic cell clones [1]. Meanwhile, there are challenging issues for the intermediate-risk AML group, which is defined as a non-homogeneous clinical entity, due to a variety of encountered gene mutations (FLT3, NPM1, CEBPA, etc.) coupled to appropriate differences in clinical course, relapse risk, and adequate treatment choice. Allogeneic transplantation of hematopoietic stem cells (allo-HSCT) was proven to be an optimal approach to AML therapy [2]. However, leukemia relapses develop in 33-78% of AML patients following allo-HSCT, mainly, due to post-treatment persistence of residual leukemic cells in hematopoietic tissues defined as minimal residual disease (MRD). Therefore, a search for new molecular markers able to predict the relapse risk in AML cases, especially those lacking evident cytogenetic abnormalities, represents a high-priority task for clinical molecular oncohematology.

In this respect, the BAALC (brain and acute leukemia, cytoplasmic) gene is a useful molecular marker showing enhanced expression in AML malignant cells, being also associated with unfavorable disease prognosis after the induction chemotherapy [3, 4, 5]. In earlier studies, the high BAALC expression level was observed as a single abnormality in AML patients associated with chromosome 8 trisomy [6]. Later on, the BAALC overexpression was shown to be a negative prognostic factor in AML patients with normal karyotype (NK-AML) [7, 8]. The cases of leukemia with primary chemoresistance, high relapse risk and lower overall survival (OS) rates were more common among the patients with BAALC over-expression, if compared to the patient groups with low BAALC expression [7, 9].

BAALC gene is located in the 8q22.3 locus (chromosome 8). In normal hematopoiesis, BAALC expression is limited by a population of early CD34+ progenitor cells, being, however, associated with the most immature blasts in acute leukemia (AL) [7, 8]. The BAALC overexpression frequency is about 40-60%, similarly to other AML expression markers. But, despite such high prevalence, the functional role of BAALC gene product was only recently specified for the leukemia pathogenesis. Morita and co-authors [10] have shown that BAALC overexpression in leukemic cell lines is associated with a cell cycle progression through the ERK-kinase intracellular signaling cascade activation. In addition, more abundant BAALC protein in the cytoplasm interacts with KLF4 transcription factor, thus causing blockage of KLF4 nuclear transport and inhibition of the specific tumor cell suppression. At the same time, a constitutive BAALC expression/activation in normal hematopoietic stem cells does not influence their proliferative activity [11]. This fact suggests that an additional genetic defect may promote AML in patients with over-expressed BAALC associated with a relapse before allo-HSCT. Ability of BAALC to block myeloid differentiation of hematopoietic stem cells, due to interaction with FosA9 oncogene, could be one of such tumor-promoting factors [11]. Hence, some recent data point to certain interrelations between the BAALC over-expression and functional changes in malignant AML cells, thus assisting the disease progression.

Interestingly, BAALC expression is regulated by the SP1/NF-kB transcription factor complex. Its pharmacological inhibitor (Bortezomib) reduces the BAALC transcripts abundance in AML cell line KG1α [12]. Suppression of BAALC expression by shRNA in KG1α cells leads to a decrease of the proliferative activity and apoptosis induction [13]. Further studying of the complex genetic abnormalities, associated with intracellular signaling in BAALC-positive AML, may assist both with selection of therapeutic approach, and opens new opportunities in targeted therapy of resistant AML and prevention of post-transplant relapses.

The aim of this study was to analyze prognostic significance of BAALC gene over-expression in AML patients during the post-transplant period, in order to estimate feasibility of BAALC expression level monitoring, to predict the relapse risk, and to evaluate sensitivity and specificity of BAALC gene expression assays, as a tool for MRD monitoring.

Patients and Methods

Clinical data

The study included ninety-three AML patients who have undergone 94 allo-HSCTs (one transplantation was repeated) at the R. Gorbacheva Memorial Institute Research Institute of Children Oncology, Hematology and Transplantation (St. Petersburg) from 2010 to 2014. A median follow-up time after HSCT was 7 (0.5 to 52.5) months. The detailed patient characteristics are shown in Table 1. Bone marrow sampling for molecular studies was performed before and after allo-HSCT on 15-720 days posttransplant.

RNA extraction and reverse transcription

RNA was isolated from the fresh bone marrow samples by the guanidine-phenol-chloroform extraction method using the “Ribo-zol-D” kit reagent (InterLabService, Russia), according to the manufacturer’s instructions.

Eleven microliters of extracted RNA were used for reverse transcription and cDNA synthesis, being performed with RevertAid First Strand cDNA Synthesis Kit (LifeTechnologies, USA).

Quantitative evaluation of BAALC gene expression

For each cDNA sample, multiplex PCR was performed for BAALC and ABL genes. The reaction conditions were as follows: 10 µl of PCR reaction mixture (“Syntol”, Russia), containing dNTP mix 2.5 mM each, 10xPCR buffer, 5 Units of Taq-DNA polymerase and 2.5µl of 25 mM MgCl2, supplemented with 7 pmol of each gene-specific primers, 5 pmol of Taqman probes for the both BAALC and ABL genes. The primer and TaqMan probe sequences for the quantitative real-time PCR are shown in Table 2. Finally, 5µl of cDNA template, or calibrator for BAALC and ABL (“Inogene”, Russia) were added to the individual tubes, at a total PCR reaction volume of 25µl. Quantitative real-time PCR was performed...
with a BioRad iQ5 instrument (“BioRad”, USA). The amplification protocol was 95°C for 10 min followed by 50 cycles of heating at 95°C (15 sec), and annealing at 60°C (1 min). The relative BAALC expression levels, or BAALC copy numbers (CN) were determined against the housekeeping reference gene ABL1 to adjust for variations in mRNA quality and different efficiencies of cDNA synthesis. [14]. The gene expression ratio was calculated by the formula CN(BAALC)/ CN (ABL)x100%, and the results were expressed in percents.

**Statistical methods**

Statistical evaluation was performed using descriptive statistics and non-parametric correlation analysis (Spearman rank correlation quotient). In order to reveal the basal BAALC cut-off expression level for MRD monitoring, the analysis of its specificity and sensitivity compared to the reference methods was calculated using ROC-analysis. The prognostic significance of BAALC expression level estimated by plotting of OS, RFS and relapse risk curves, according to Kaplan-Meier. SPSS software version 22.0 (IBM corporation, Armonk, NY, USA) and SAS9 were used for statistical analysis.

**Results**

**Correlation between BAALC expression level and clinical scores**

In the present study, we have observed positive correlations between BAALC expression level and the number of blast

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**Table 1. Clinical characteristics of the patients**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Number of cases (Percentages of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient number</td>
<td>93</td>
</tr>
<tr>
<td><strong>BAALC status pre-transplant:</strong></td>
<td></td>
</tr>
<tr>
<td>BAALC-positive AML</td>
<td>15 (16.1%)</td>
</tr>
<tr>
<td>BAALC-negative AML</td>
<td>19 (20.4%)</td>
</tr>
<tr>
<td>Not determined</td>
<td>59 (63.5%)</td>
</tr>
<tr>
<td>Age, years; median</td>
<td>2-60; 26</td>
</tr>
<tr>
<td>Sex; male/female</td>
<td>44/49</td>
</tr>
<tr>
<td><strong>FAB classification</strong></td>
<td>M0 – 6 (6.5%), M1 – 13 (14%), M2 – 19 (20.4%), M3 – 2 (2.2%), M4 – 29 (31.2%), M5 – 12 (12.9%), M7 – 1 (1.1%), unspecified FAB – 11 (11.7%)</td>
</tr>
<tr>
<td><strong>Cytogenetic characteristics in AML debut</strong></td>
<td></td>
</tr>
<tr>
<td>t(8;21)</td>
<td>9 (9.7%)</td>
</tr>
<tr>
<td>inv(16)</td>
<td>5 (5.4%)</td>
</tr>
<tr>
<td>t(15;17)</td>
<td>3 (3.2%)</td>
</tr>
<tr>
<td>Normal karyotype</td>
<td>62 (66.7%)</td>
</tr>
<tr>
<td>Other cytogenetic abnormalities</td>
<td>10 (10.7%)</td>
</tr>
<tr>
<td>Complex karyotype</td>
<td>4 (4.3%)</td>
</tr>
<tr>
<td><strong>Type of allo-HSCT:</strong></td>
<td></td>
</tr>
<tr>
<td>Related donor</td>
<td>16 (17.2%)</td>
</tr>
<tr>
<td>Unrelated</td>
<td>67 (72%)</td>
</tr>
<tr>
<td>Haploidentical</td>
<td>10 (10.8%)</td>
</tr>
<tr>
<td><strong>Conditioning regimen:</strong></td>
<td></td>
</tr>
<tr>
<td>Myeloablative</td>
<td>33 (35%)</td>
</tr>
<tr>
<td>Nonmyeloablative</td>
<td>60 (65%)</td>
</tr>
<tr>
<td><strong>Relapses after allo-HSCT, n (%):</strong></td>
<td>27 (28%)</td>
</tr>
</tbody>
</table>

**Table 2. Sequences of primers and TaqMan probes used in this work**

<table>
<thead>
<tr>
<th>Gene studied</th>
<th>Forward primers</th>
<th>Reverse primers</th>
<th>TaqMan fluorescent probes</th>
</tr>
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<tbody>
<tr>
<td>BAALC</td>
<td>5’-CTACAGCCCCCAGGTGAATA-3’</td>
<td>5’-TTGCAGGCATTCTCTTAGCA-3’</td>
<td>(FAM)-ATGGCCCTCAGACCACAGAG-(BHQ2)</td>
</tr>
<tr>
<td>ABL</td>
<td>5’-TGGAGATAACACTCTAGCATAAACTAAGGT-3’</td>
<td>5’-GATGATGTTGCTTGGGACCACCA-3’</td>
<td>(JOE)-CCATTTTTTGGGCTTCACACATT-(BHQ1)</td>
</tr>
</tbody>
</table>
cells in bone marrow (R=0.417, N=93, p=0.000), and with chimeric transcripts in the favorable cytogenetic risk group (RUNX1-RUNX1T1, PML-RARα and CBFB-MYH11) (R=0.388, N=16, p=0.000). A stronger correlation was revealed between BAALC and chimeric transcript RUNX1-RUNX1T1 expression (R=0.521, N=9, p=0.000). Besides, in three patients, who displays PML-RARα transcript, we observed relative lower BAALC expression profile (BAALC expression level ranged from 0.05% to 12.87% with a median 1.84%). In addition, a negative correlation was revealed for BAALC and donor chimerism level which was determined by analysis of short tandem repeats (R= -0.257, N=93, p=0.0001).

Posttransplant BAALC expression monitoring for the relapse risk estimation

The terms of relapse for the patients included into this study ranged from 24 to 400 (a median of 101) days post-transplant. BAALC expression level in the cases of posttransplant relapse was higher than in non-relapsing patients, except for the early posttransplant period (Fig. 1). The most significant difference was detected at D+60 (p=0.006), D+90 (p=0.022), D+120 (p=0.008), D+150 (p=0.006), and D+270 (p=0.006) after allo-HSCT.
In 88.2% patients with relapse, we observed BAALC expression level of more than 0.5 log_{10} above the individual threshold. Moreover, a rise of individual BAALC expression levels by more than one order of magnitude was registered in 80% of post-transplant relapsed patients. Such an increase was not observed in patients with relapse-free post-transplant course. Therefore, BAALC overexpression of >1 log_{10} has been chosen as an individual cut-off level for studying prognostic significance of BAALC during the post-transplant period in AML patients.

BAALC overexpression: prediction for survival and relapse risk

In the study group, expression of BAALC above the cut-off level of 60% was observed in 51.9% of relapse cases (14 of 27 patients), whereas individual increases over the cut-off value were registered in 11 relapsed patients of 14 (78.6%).

When studying the prognostic significance of BAALC over-expression, we have revealed significant correlations between both individual and common cut-off excess and overall survival, relapse-free survival and relapse risk over a 2-year period after HSCT (Fig. 4). In cases of BAALC over-expression > 60%, both OS and RFS rates were decreased to 7.1% and 0%, respectively, and the relapse risk was 100%. In case of BAALC over-expression above 1 log_{10} higher than individual cut-offs, the OS and RFS factors were 11.1% and the relapse risk was 88.9%. In particular, BAALC overexpression by >1 log_{10} over individual cutoff allows assignment of the patients to prognostically unfavorable risk group for high OS, RFS and relapse risk (Fig. 5).

Moreover, we have revealed that the pre-relapse increase of individual cutoff values proved to occur sooner than an increased common cut-off value (>60%).

For example, BAALC expression by more than 1 log_{10} over individual basal expression levels was observed in 6 of 14 relapse cases in this group (42.9%) and it developed at 51 days (3-115) prior to clinical relapse. BAALC expression of >60% before the clinical relapse was registered in 2 cases from 21 (9.52%), and in both cases it was developed in 9 days before clinical symptoms of relapse.

Assessing the BAALC cut-off level for reliable MRD monitoring

Minimal residual disease (MRD) is one of basic reasons of posttransplant relapses in AML. The most sensitive method for MRD detection is the monitoring of the patient-specific cytogenetic aberrations in leukemic cells, resulting in fusion transcripts, or genetic point mutations. However, more than a half of AML patients lack such informative genetic markers [15]. Such patient cohorts represent an ideal group for studying the significance of BAALC overexpression for MRD detection and estimation of relapse risk in post-transplant period.

Our study included assessment of cut-off level for BAALC expression aimed for MRD monitoring in the patients with chimeric transcripts. Appropriate expression levels were based on results of quantitative real-time PCR (N=17). By comparing BAALC expression in molecular remission (MRD=0%) and relapse (MRD>0%) using the receiver-
operating characteristic curve (ROC) plotting method, a range of the most sensitive and specific cut-off level values was determined for clinical relapse prediction (Fig. 6A). The area under the curve (AUC) was 0.698. The BAALC expression level at maximal sensitivity and specificity for detection of residual tumor cell was adjusted to 5.2% (sensitivity of 0.495, and specificity of 0.914).

Using the generated cut-off value of 5.2% for the entire patient cohort, we have shown that the BAALC expression exceeding such value did not significantly influence the relapse risk (p=0.071), overall (p=0.422) and relapse-free survival (p=0.244) after the HSCT (Fig. 6 B-D).

At the same time, the amounts of positive chimeric gene transcripts in favorable-risk patient group (N=17) ranging from 0.002 to 231%, with a median of 0.09%, were observed at the BAALC<5.2% expression level (Fig. 7).

Discussion

Our study aimed for evaluation of prognostic significance for the BAALC overexpression after allo-HSCT, as well as BAALC monitoring for relapse risk estimation after HSCT, and calculation of sensitivity and specificity indexes of MRD testing in AML patients with normal karyotype.

We have found positive correlations between BAALC expression levels and amounts of blast cells in bone marrow samples, and correlations with molecular cytogenetic markers in favorable AML risk group, especially, with chimeric RUNX1-RUNX1T transcript. These data well conform to the previously published analyses [16]. The low correlation quotient may be explained by the fact that BAALC expression is more typical to the least differentiated hematopoietic progenitors and blast cells that express the CD34 surface marker. However, leukemic cells in 20% of AML cases are more differentiated, being CD34-negative, thus exhibiting...
Figure 6. Graph A: estimation of basal BAALC cut-off level for MRD detection by means of ROC-analysis; B, influence of BAALC overexpression (BAALC>5.2%) on the clinical relapse risk in AML patients with normal karyotype (NK-AML) after allo-HSCT; C, influence of BAALC overexpression (BAALC>5.2%) on the 2-year OS values of NK-AML patients; D, influence of BAALC overexpression (BAALC>5.2%) on the 2-year RFS values of NK-AML patients after HSCT.

Figure 7. Expression range of mRNA fusion transcripts typical to favorable cytogenetic risk group at the BAALC expression levels of <5.2%.
lower BAALC expression [7, 17, 18]. Stronger correlation of BAALC and RUNX1-RUNXIT1 compared to other translocations in favorable cytogenetic group can be explained by the presence of a G424T polymorphism (rs62527607) in BAALC promoter region which is found in 15% of cases. This nucleotide substitution creates an additional site for high affinity RUNX1 transcription factor binding [19, 20]. The RUNX1 transcription factor and RUNX1-RUNXIT1 chimeric protein have a similar target gene activation profile, due to identical DNA-binding domain structure, thus potentially leading to increased BAALC expression by the RUNX1-RUNXIT1 in cases of 424T allele [21]. Additional experiments are required to confirm this hypothesis.

A negative correlation between the BAALC expression level and PML-RARa fusion transcript was also discussed previously. BAALC expression level is significantly lower in acute promyelocytic leukemia (APL), exhibiting a specific PML-RARa translocation [22, 23]. A functional role of BAALC gene in APL induction is still open to debates. However, BAALC overexpression allows to distinguish a sub-group with unfavorable disease prognosis within the high-risk APL cohort [23, 24].

According to several studies, BAALC overexpression above both individual and common cut-off levels is recognized as a prognostically significant factor for posttransplant relapse risk estimation, overall survival and relapse-free survival. Interestingly, in the cases of BAALC-positive AML status before HSCT, this marker remained to be informative in 89% of posttransplant relapses (8 from 9 cases). Overexpression of WT1 and PRAME markers in the exceptional BAALC-positive case was observed in the bone marrow sample at the posttransplant relapse. This fact is absolutely consistent with literature data [25], where BAALC gene expression is discussed as an early event in the dominant clone, which remains relatively stable through clonal evolution.

We have also used studied individual threshold values of BAALC expression before transplant, in order to predict a risk of clinical relapse after allo-HSCT. A ten-fold increase of individual BAALC expression over the median has been chosen as a cut-off value for results obtained in clinical remission before HSCT. Elevation over general cut-off value of 60% correlated with maximal risk of clinical relapse during the 1st year post-transplant. Increased BAALC expression by one to four log_{10} (10-10 000 fold) over individual cut-off values suggested a transfer of the patient to unfavorable risk group. A feasibility of the individual BAALC expression monitoring is confirmed by increased expression of BAALC over general cut-off levels in only 51.9% of relapsed patients, whereas individual thresholds were exceeded at earlier terms before relapse, being informative in 78.6% of relapses. Such findings are in accordance with the literature data, where only 53.9% of relapsed patients had BAALC/ABL1 ratio over than 60% [25].

Referring to the scientific publications, monitoring of the BAALC expression may be useful for therapy efficiency estimation in the patients lacking specific genetic markers of tumor cells, and for prediction of molecular and clinical relapse [4, 22, 25, 26]. Applicability of BAALC expression as a MRD marker is based on its sufficient overexpression in relapse if compared to the remission values and its correlation with gene expression of AML markers, such as RUNX1-RUNXIT1, WT1 expression, other markers of normal-karyotype AML (RUNX1, FLT3-ITD, NPM1, CEBPA, MLL-PTD etc.). Our data confirm a significant difference of BAALC expression for the remission and relapse states. However, a more detailed analysis of BAALC as an MRD marker, and its comparison to the reference techniques for MRD monitoring (i.e., qPCR-based detection of chimeric gene transcripts) was performed, showing lower sensitivity of such approach to MRD detection in post-transplant period, at least, for our study group. In the absence of BAALC overexpression (BAALC>5.2%), positive MRD values can be observed, whereas BAALC over-expression (BAALC>5.2%) did not significantly correlate with relapse risk, overall and relapse-free survival. Therefore, quantitative monitoring of BAALC expression could not be recommended as a universal marker of therapy efficiency in the patients with normal-karyotype AML after allo-HSCT, since a specificity of BAALC for CD34+ leukemic blasts is reduced, due to its basal expression in early hematopoietic progenitors [7, 27].

Conclusion

Summarizing our results obtained with a representative group of AML patients, we may recommend the serial quantitative BAALC monitoring for clinical relapse prediction following allogeneic hematopoietic stem cell transplantation. Tracing of BAALC expression levels and individual assignment of cut-off values can be useful not only for stratification of patients into different risk groups, but also for selection of appropriate AML therapy after allo-HSCT.

Conflict of interest

No conflicts of interest are reported.

References


Clinical Studies


Прогностическое значение гиперэкспрессии BAALC у больных острым миелобластным лейкозом в посттрансплантационном периоде

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Резюме

Острый миелобластный лейкоз (ОМЛ) представляет собой гетерогенное клональное заболевание крови опухолевой природы. Для пациентов с ОМЛ промежуточной цитогенетической группы риска, которая является гетерогенной по мутационному статусу целого ряда генов (FLT3, NPM1, CEBPA и т.д.), прогнозирование течения заболевания, оценка риска развития рецидива и выбор оптимальной терапии затруднены. В связи с этим поиск новых молекулярных маркеров, имеющих большое прогностическое значение, а так же полезных в аспекте оценки риска развития рецидива у пациентов с ОМЛ, лишенных крупных цитогенетических аномалий, является одной из приоритетных задач молекулярной онкогематологии. Для оценки применимости мониторинга уровня экспрессии гена BAALC (Brain And Acute Leukemia, Cytoplasmic) для предикции развития рецидива у пациентов с ОМЛ, мы проанализировали прогностическое значение гиперэкспрессии гена BAALC у 93 пациентов с ОМЛ в посттрансплантационном периоде. Мы заключили, что гиперэкспрессия BAALC у пациентов с ОМЛ в посттрансплантационном периоде является прогностически значимым фактором для оценки риска развития рецидива в посттрансплантационном периоде, общей и безрецидивной выживаемости. Однако более детальный анализ BAALC как маркера эффективности терапии и его сравнение с референтными методами мониторинга минимальной остаточной болезни (такими как детекция химерных транскриптов генов методом количественной ПЦР в режиме реального времени) показал более низкую чувствительность такого подхода к мониторингу МОБ в посттрансплантационном периоде, по меньшей мере на примере исследуемой выборки пациентов.

Ключевые слова

Острый миелобластный лейкоз, BAALC, экспрессия гена, клинический прогноз, минимальная остаточная болезнь.